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Sedation versus general anaesthesia in endovascular therapy for anterior circulation acute ischemic stroke: the multicentre randomised controlled AMETIS trial study protocol

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ARTICLE FOCUS

Endovascular thrombectomy is now the cornerstone in treatment of large anterior circulation acute ischemic stroke. Nevertheless, we still don't know which procedural anaesthetic management is better since conflicting results exist between outcomes associated with Conscious Sedation (CS) and General Anaesthesia (GA). The anaesthetic management could influence the overall evolution and functional independence in these frail patients.

We therefore designed a multicentre prospective randomised controlled trial to evaluate outcomes associated with GA and CS in anterior circulation AIS. The primary outcome measure will be a composite of functional independence at 3 months and absence of medical complications occurring by day 7 after thrombectomy.

KEY MESSAGES

To our knowledge, this is the first multicenter randomised controlled trial investigating outcomes associated with CS and GA for thrombectomy in anterior circulation acute ischemic stroke.

ABSTRACT

Introduction: Endovascular thrombectomy is the standard of care for anterior circulation acute ischemic stroke (AIS). To ensure patient comfort, security and treatment efficacy Conscious Sedation (CS) or General Anaesthesia (GA) could be proposed. Nevertheless, regarding functional outcomes, we still don't know which anaesthetic strategy is better. Indeed, conflicting results exist between observational studies with better outcomes associated with CS and small monocentric randomized controlled trials favouring GA. Therefore, we aim to evaluate the effect of CS versus GA on functional outcome and peri-procedural complications in endovascular mechanical thrombectomy for anterior circulation AIS.

Methods and analysis: Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is an investigator initiated, multicentre, prospective, randomised controlled, two-arm trial. AMETIS trial will randomised 270 patients with anterior circulation AIS in a 1:1 ratio, stratified by centre, NIHSS (≤ 15 or > 15) and association of intravenous thrombolysis or not to receive either CS or GA. The primary outcome is a composite of functional independence at 3 months and absence of medical complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Medical complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or cardiogenic acute pulmonary oedema or malignant stroke evolution occurring by day 7.

Ethics and dissemination: The AMETIS trial was approved by an independent ethics committee. Study began in august 2017. Results will be published in an international peer-reviewed medical journal.

Trial registration number: NCT03229148.

(Abstract word count: 242)

ARTICLE SUMMARY

Strengths and limitations of this study

- Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is the first multicentre randomised controlled trial comparing conscious sedation (CS) and general anaesthesia (GA) in thrombectomy for anterior circulation (internal carotid artery and/or proximal middle cerebral artery) acute ischemic stroke.
- The multicentre setting and large pragmatic inclusions criteria compatible with current practice and recommendations will allow external validity.
- Stratification based on centre, stroke severity and concomitant administration of intravenous thrombolysis will allow groups homogeneity and comparability.
- Composite primary outcome measure will allow evaluation of functional independence at 3 months and neurological and non-neurological peri-procedural complications. Secondary outcomes will measure different important aspects of care.
- Despite the absence of specific anaesthetic protocol concerning CS and GA management in order to reinforce external validity, perfusion pressure determinants (arterial blood pressure and carbon dioxide tension) will have to be maintained in strict limits.

INTRODUCTION

Background and rationale

Endovascular mechanical thrombectomy dramatically changed management of acute ischemic stroke (AIS). Randomised controlled trials demonstrated improved outcome associated with the procedure using stent-retrievers in anterior circulation AIS.[1-6] The American Heart Association/American Stroke Association, as others national medical societies, rapidly endorsed this strategy as a level 1 recommendation in association if possible with intravenous thrombolysis.[7] Nevertheless, peri-procedural management in the field added complexity since immobility and cardio-respiratory stability could be incompatible with acute neurological failure in these frail patients. Notably, anaesthetic management precludes debate since 2 strategies could be proposed: conscious sedation (CS) and general anaesthesia (GA). It was traditionally assumed that CS was superior since GA could negatively affect brain physiology especially cerebral blood flow (CBF) in the penumbra area related to induced systemic hypotension and carbon dioxide modulation.[8] Also, it was stressed the possible excessive delay associated with GA initiation that counteract a "time is brain" strategy. Nevertheless, evidence based medicine supporting this concept is scarce with methodological issues associated with observational data.[9] Notably, sickest patients were prone to receive GA and the anaesthetic strategy was not protocolized nor randomised.[10] We could conceptually argue possible benefits of GA providing systemic hypotension is treated and avoided: 1) immobility that could facilitate an easier, rapid and effective technical procedure, 2) airway protection since AIS patients are prone to aspiration pneumonia related to neurological injury, 3) patient comfort in a highly stressful environment with sometimes prolonged procedures.[9] Recently, 3 small monocentric randomised controlled trials specifically addressed effect of anaesthesia care on stroke outcome. First, the SIESTA trial randomised 150 patients between CS and GA.[11] No difference occurred in the National Institutes of Health Stroke Scale (NIHSS) at 24 hours, which was the primary

outcome. More patients were functionally independent after 3 months, defined as a Modified Rankin Scale (mRS, which ranges from 0 [no symptom] to 6 [death]) score 0 to 2, in the GA group. Second, the AnStroke trial randomised 90 patients between CS and GA.[12] No difference was achieved concerning the primary outcome mRS at 3 months and others secondary outcomes. Finally, the GOLIATH trial randomised 128 patients between CS and GA.[13] There was no difference in the volume of infarct growth as a primary outcome despite significantly higher successful reperfusion and better mRS score at 3 months in the GA group. On the assumption of these discrepancies, a multicentre randomised controlled trial comparing CS and GA is urgently needed.[14,15]

Objectives

Primary objective

The primary objective of the study is to determine whether CS or GA is associated with improved outcome defined as a composite of functional independence at 3 months and absence of medical complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Medical complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or cardiogenic acute pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary objectives

The study will also explore if CS or GA in endovascular therapy for anterior circulation AIS is associated with difference in several outcomes: functional independence by day 90, intraprocedural hemodynamic and ventilatory conditions, intervention-associated vessel and others complications, door to groin puncture delay, door to reperfusion delay, successful

recanalization, stroke unit and hospital length of stay, medical complications by day 7, unexpected intensive care unit admission by day 7, mortality by day 7 and day 90.

Trial design

The Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is an investigator initiated, national, multicentre, prospective, open-labelled, stratified, randomised controlled two-arm trial.

Consort diagram

Figure 1 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram of the AMETIS trial.[16]

METHODS AND ANALYSIS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

This manuscript was written in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (supporting file in the appendix).[17]

Study setting

The AMETIS trial takes place in 11 university hospitals in France (Clermont-Ferrand, Paris Pitié-Salpêtrière, Paris Saint-Antoine, Lyon, Toulouse, Marseille, Montpellier, Rouen, Lille, Poitiers and Saint-Etienne).

Eligibility criteria

Inclusion criteria

Adult patients admitted for anterior circulation (internal carotid artery and/or proximal middle cerebral artery) AIS, eligible for thrombectomy as decided by the neurology/neuroradiology teams based on current guidelines using brain imaging selection.[15]

Exclusion criteria

Patients with one or more criteria are not included:

- Age < 18 years.
- Coma or altered vigilance defined as a score ≥ 2 on the level of consciousness 1A subscale of the NIHSS.[18]
- Premorbid loss of autonomy defined as a mRS > 1.[19]
- Posterior circulation stroke.
- Associated cerebral haemorrhage.
- Stroke complicating another acute illness or postoperative stroke.
- Pregnant or breastfeeding women.
- Adult under the protection of the law.

Interventions

Patients eligible for inclusion will be randomly assigned to CS or GA.

Modality of the CS and GA protocols are left to the attending anaesthesiologist in accordance with current and local guidelines providing systolic blood pressure is maintained between 140 and 180 mmHg (with vasopressor infusion if necessary) and arterial pulse oxymetry (SpO2) > 94 %.[15]

Under GA, tracheal intubation is mandated and mechanical ventilation should be managed to maintain an End Tidal CO2 (EtCO2) level between 30 and 35 mmHg.

Under CS, a minimal to moderate sedation level has to be targeted as defined by the American Society of Anesthesiologists (ASA) recommendations.[20] Clinical sedation level will be evaluated using the Richmond Agitation Sedation Scale (RASS) with an objective between 0 and -3 (defined as a patient alert and calm or drowsy with sustained awakening (eye opening/eye contact) to voice ≥ 10 seconds or briefly awake to voice with eye contact < 10 seconds or movement/eye opening to voice).[21,22] Effective spontaneous ventilation has to be maintained.

In the CS group, a crossover to GA with tracheal intubation is recommended in case of severe agitation, coma defined as a -4 or -5 RASS value (no response to voice but movement or eye opening to physical stimulation or no response to physical stimulation) despite stopping sedative drugs, loss of airway protective reflexes, respiratory failure and incoercible vomiting.

Stent retrievers are the preferred devices to perform thrombectomy. Nevertheless, alternative devices could be used.

At the end of intervention, GA and CS have to be immediately stopped and in the GA group extubation should occur as soon as possible.

After the intervention, depending on each hospital organization and anaesthesia modality (GA or CS), patients are transferred to the post anaesthesia care unit or neurological or general intensive care unit.

Outcomes

Primary outcome measure

The primary outcome measure is a composite of functional independence at 3 months and absence of medical complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Medical

complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary outcome measures

- mRS by day 90[19,23,24]
    - Ordinal score on the mRS by day 90
    - Functional independence by day 90 defined as a mRS score 0-2
    - Excellent recovery by day 90 defined as a mRS score 0-1
    - Moderate recovery by day 90 defined as a mRS score 0-3
    - Shift analysis of day 90 mRS adjusted for initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion)
    - Good recovery defined with sliding dichotomy responder analysis relating day 90 mRS with baseline NIHSS score: mRS 0 for NIHSS ≤ 7; mRS 0-1 for NIHSS 8-14; mRS 0-2 for NIHSS > 14
- Intraprocedural hemodynamic and ventilatory conditions and complications defined as hypotension, blood pressure variability, hypoxemia and aspiration
- Intervention-associated vessel and others complications defined as arterial dissection or perforation, groin hematoma, embolization in another arterial territory
- Door to groin puncture delay
- Door to reperfusion delay
- Successful reperfusion defined by the modified Treatment In Cerebral Ischemia (mTICI) reperfusion scale of 2b or 3 (with a grade of 2b or 3 indicating reperfusion of > 50% of the affected territory)[25]
- NIHSS by day 1 and day 7[18]

- Stroke unit and hospital length of stay
- Medical complications by day 7 defined as pneumonia, acute cardiogenic pulmonary oedema, myocardial infarction, extra pulmonary infection, venous thromboembolism, new event of AIS, epilepsy, gastrointestinal bleeding or other symptomatic bleeding[26]
- Malignant stroke evolution by day 7[27]
- Symptomatic intracranial haemorrhage by day 7 defined as brain haemorrhage on imaging associated with an increase of at least 4 points in the NIHSS score[28]
- Unexpected intensive care unit admission by day 7
- Mortality by day 7 and day 90
- Procedural feasibility score estimated by the radiologist and the anaesthesiologist and patient acceptability score[29]

Recruitment

Patients are expected to be included during a 2-year period starting in august 2017.

2016-2017: Protocol, approvals from ethics committee (*CPP Sud-Est I*) and the French Medicine Agency (*Agence Nationale de Sécurité du Médicament et des produits de santé, ANSM*); trial tool development (online case report form and randomisation system).

2017-2019: Inclusion of patients.

2019: cleaning and closure of the database, data analyses, writing of the manuscript and submission for publication.

Trial status

The current protocol is version 4.0. Study started enrolment in august 2017. To date (28th October 2018), 186 patients have been randomised in the study.

Patient and public involvement

Patients will not be invited to comment on study design or conduction of the trial.

METHODS: ASSIGNEMENT OF INTERVENTIONS

Allocation and sequence generation

Randomisation will be conducted over a dedicated password-protected, SSL-encrypted website (CSOnline, Clinsight) to allow concealed allocation. Each patient will be given a unique patient number and randomisation number. The allocation sequence will be generated with the use of a minimisation algorithm stratified according to centre, NIHSS score (≤ 15 or > 15) and association of intravenous thrombolysis or not. The participant allocation will be carried out by local investigators who will log into the randomisation system using a personal ID and will enter any relevant information.

Blinding

This is an open label, unblinded trial for the patient and the physician in charge, related to the nature of the intervention (GA with endotracheal intubation or CS). Assessor blinded evaluation of the primary outcome will be performed since the assessor and statistician will be masked to the subjects' assignment group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

At each participating centre, data will be collected and entered into the web-based electronic case report form (eCRF) (CSOnline, Clinsight) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators. From the eCRF, the trial database will be created. Paper case report form will be

used in case of technical problems with the eCRF. Trained research coordinators will monitor data collection. Data collected are presented in supplementary file 1.

Patient withdrawal:

Evaluated procedure is tested during endovascular thrombectomy. Nevertheless, participant can withdraw consent at any time without need for further explanation. Data will be destroyed and a new patient will be randomised for the complete sample size.

Statistical methods

Sample size estimation

According to literature analysis based on 5 international randomised controlled trials about endovascular thrombectomy in anterior circulation AIS, frequency of events constitutive of the composite primary outcome was expected at 50%[1-5]. Then, we postulated that 124 patients per group would provide 90% statistical power to detect an absolute between-group difference equals 20% (50% vs. 30%) for a two-sided type I error at 5%. Assuming lost to follow-up and modified intention to treat population requirements (as defined in supplementary file 2) of 10%, 270 patients have to be recruited for the study.

Interim analysis

A safety interim analysis is planned after 50% of inclusions. The independent Data and Safety Monitoring Board (DSMB) could recommend stopping the study if prolongation of the trial clearly compromises patient safety (in case of serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs)). The steering committee (SC) will be responsible to continue, hold or stop the study based on the DSMB recommendations.

Statistical analysis

A predefined statistical analysis plan will be followed (supplementary file 2). All analyses will be conducted with Stata software (version 13, StataCorp, College Station, USA) and R (http://cran.r-project.org/) before the breaking of randomisation code, in line with the International Conference on Harmonization Good Clinical Practice guidelines. A two-sided p value of less than 0.05 will be considered for statistical significance.

Primary analysis will be done in modified intention to treat (mITT). Then, a per-protocol analysis will also be done to take into account protocol deviations notably crossover from CS to GA. Patients who withdraw consent will not be included in these analyses.

Continuous variables will be presented as mean and standard-deviation or as median and quartiles otherwise. Normality will be assessed using the Shapiro-Wilk test and homoscedasticity will be assessed using the Fisher-Snedecor test.

Concerning the comparison of the primary composite outcome between CS and GA, a Chi2 test or a Fischer's exact test will be performed as appropriate. Adjusted analysis will be conducted with the use of robust random-effects Poisson generalised linear regression will be used (1) to take into account adjustment on possible confounding covariates selected according to clinical relevance and stratification variables (including stratification parameters) and (2) to consider within and between centre variability (as random-effect). The results will be presented as relative risks and 95% confidence interval (CIs). The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome.

Concerning the comparisons of secondary outcomes between groups, Student t test or non-parametric Mann-Whitney test as appropriate will be used for quantitative parameters such as intraoperative blood pressure, oxygen saturation, timing delays or length of stays. Chi-squared test or Fischer's exact test will be used for categorical parameters such as NIHSS and ordinal and nominal (dichotomized) mRS, intervention-associated and medical complications, mTICI

score, functional independence at day 90 and mortality. Results will be reported as effect-sizes and absolute differences with 95% CIs. Then, multivariable analyses will be conducted using random-effects models taking into account between and within centre variability: linear mixed models for quantitative endpoints and generalized linear mixed regression for categorical endpoints. The results will be expressed, respectively, as regression coefficients and relative risks, with 95% CIs.

Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure, this parameter will be treated by different ways according to literature notably as an ordinal variable.[15,30] A shift analysis will also be performed: Cochrane Mantel–Haenszel for the univariate analysis and random-effects ordinal logistic regression adjusted on initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion) for multivariable analysis.

Time-to-event curves will be calculated with the use of the Kaplan-Meier method in univariable analysis. For multivariable analysis, marginal Cox proportional hazards model (with centre as random effect) will be performed. Proportional hazard assumption will be verified using the Schoenfeld test and plotting residuals. Results will be reported as HRs with 95% CIs.

Concerning the study of parameters collected longitudinally (in particular NIHSS score at day 1 and day 7, arterial pressure and arterial oxygen saturation), mixed models will be used to take into account between and within patient variability, in addition to centre random-effect. The following fixed effect will be analysed: randomisation group, time and their interaction (time x group).

According to clinical relevance and to European Medicines Agency (EMA) and Consolidated Standards of Reporting Trials (CONSORT) recommendations, post-hoc analyses will be proposed after the study of subgroup × randomisation group interaction in regression models (for repeated data or not).

Missing values will be notified and analysed. A sensitivity analysis will be performed and the

nature of missing data will be studied (missing at random or not). If the frequency is > 5%, additional analyses will be performed using the multiple imputation method. [31]

METHODS: MONITORING

Data monitoring

Before the start of the study, anaesthetic, neurological and radiological medical and paramedical teams are trained at each site for the study protocol by study coordinators. Physicians are in charge of patient screening and inclusion. Patients admitted for stroke treated by endovascular mechanical thrombectomy and not included in the study will be recorded anonymously at each centre into a screening log. Data will be collected in a web-based eCRF by trial personnel. Each centre will only have access to site-specific data. Each patient will receive a unique trial identification number. Only the investigators and research team will have access to any protected health information of study participants and any study data.

Data monitoring and quality control will be conducted in each centre after the first 10 inclusions then after the next 20 inclusions and at the end of the study by official representatives of the study promoter (Department of Clinical Research and Innovation, Clermont-Ferrand University Hospital).

Data will be handled according to the French law. All originals records (including consent forms, reports of SUSARs and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years. Only the principal investigators and the statistician will have access to the final dataset.

Harms

Every adverse events that could be related to the trial will be reported to the trial coordinating centre. According to the French law, all suspected serious adverse events will be reported to the ANSM. The DSMB will also be informed. DSMB is independent from the trial investigators and will perform an ongoing review of safety parameters and study conduct. DSMB members are 2 independent physicians in Anaesthesia / Critical Care Medicine and Neurology, and a Biostatician that have skills and expertise in Anaesthesia, clinical Neuroscience and clinical research. The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety of the interventions during the trial and for monitoring the overall conduct of the trial. DSMB could also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. No formal criteria are set to stop the study. However, recommendations for pausing or stopping the study could be made by DSMB in case of SARs and SUSAR. The scientific committee will be responsible for promptly reviewing the DSMB recommendations and to decide whether to continue, hold or stop the study, and to determine whether amendments to the protocol are needed.

ETHICS AND DISSEMINATION

Research ethics approval

The AMETIS study is conducted in accordance with the Declaration of Helsinki and was registered at http://www.clinicaltrial.gov on 25 July 2017 and last updated on 5 September 2017 with trial identification number NCT03229148. The trial was approved by the ethics committee *CPP Sud-Est I* on 22 May 2017 (approval number 2017-11) and ANSM on 6 march 2017 (approval number 2016-A02064-47). Any change to eligibility criteria, outcomes and analyses will be communicated to investigators, the ethics committee and the ANSM to obtain their approval.

Consent or assent

Whenever possible to include the patient, written inform consent will be searched. Nevertheless, related to neurological injury and emergency, the patient may be unable to provide written informed consent. In this case, written informed consent could be obtained from the patient next of kin if immediately available. Otherwise, an emergency consent procedure is used with investigator signature countersigned by an independent physician. As soon as possible after recovery, written informed consent from the patient will be searched to continue the study. This consent strategy was approved by the Institutional Review Board and the ethics committee *CPP Sud-Est I* on 22 May 2017 in accordance with the 2013 Declaration of Helsinki.

Funding

The study is an investigator-initiated trial with study promotion performed by Clermont-Ferrand university hospital, Clermont-Ferrand, France. There is no industry support or involvement in the trial. This study is supported by grants from the French Ministry of Health (Projet Hospitalier de Recherche Clinique Interrégional 2016). The funders have no influence on study protocol, conduct and results analysis.

Dissemination policy

On study completion, manuscript will be submitted to one peer-reviewed journal regardless of the results. All trial sites will be acknowledged and every investigators name will appear under "AMETIS trial group" in an appendix to the final manuscript. AMETIS study scientific committee will grant authorship depending on personal input according to the Vancouver guidelines. If a trial site investigator is to gain authorship, the site has to include 30 patients or more. If the site includes 50 patients or more, two authorships will be granted. A writing committee will be composed of members of the scientific committee and investigators to define

the order of authors of any publications. Trial results will also be presented at local, national and international meetings.

DISCUSSION

We recently observed the "thrombectomy revolution" in anterior circulation AIS.[32] Emergency interventional procedures in frail stroke patients often require skills from Anaesthesia providers since immobility is needed and severe intra-procedural complications may occur (for example coma, agitation or aspiration pneumonia).

Taking into account the increasing volume of procedures and the potential effect of the anaesthetic strategy on outcome with discrepancy in literature, it appears essential to provide a multicentre randomised controlled trial to enhance external validity as suggested by recent recommandations.[15]

Some limitations could be opposed to the AMETIS trial protocol. First, no specific anaesthetic protocol will be used. We choose this strategy in a pragmatic way since no data demonstrate that a drug is better than another even if modulation of CBF could be variable. However, the protocol requires strict objectives for systolic blood pressure and "normal" blood carbon dioxide tension in GA group.[33,34] Drugs and dose will be monitored. Second, no maximal time delay from stroke onset or maximal/minimal NIHSS values are recommended in order to adhere to a pragmatic investigator-based approach. This strategy complies with recent trials and recommendations: patient selection for thrombectomy is made on angioCT or MRI scans with eventual mismatch evaluation especially when delay is > 6 hours and for wake-up strokes.[15,35,36] Delays and imaging modality used for selection will be monitored. Stratification on NIHSS score with a cut-off of 15 will provide homogeneous groups in term of initial severity. As recommended, outcome measures will include adjustments for baseline severity.[15] Third, we choose a composite principal outcome measure since anaesthesia strategy could affect

functional independence at 3 months but also peri-interventional morbidity. The effect size that we could expect on functional independence at 3 months is probably far less than thrombectomy on its own. Based on actual literature, SIESTA trial found dramatically decreased functional independence associated with CS with only 18% of mRS 0-2 compared to 37% in GA.[11] 18% of patients being independent is far less than in thrombectomy trials where it barely represents controlled groups (intravenous thrombolysis alone).[1-6] With these proportions, 240 patients would have been necessary to demonstrate a statistical difference with a beta power of 90% but we could expect important centre effect in SIESTA trial. On the contrary, ANSTROKE trial didn't find any difference between groups, with functional independence in respectively 42 and 40% of patients between GA and CS.[12] Based on these 2 trials, functional independence could be obtained in roughly 40% of patients under GA. Providing a 20% variation in positive or negative effect on functional independence, more than 1000 patients would be required with a 80% beta power. An anaesthesia size effect of more than 20% appeared unrealistic.

Fourth, even if possible in selected patients, we will not study local anaesthesia alone. Management solely under local anaesthesia is difficult regarding comfort and immobility particularly in sickest patients, in left hemisphere strokes with aphasia and in tandem lesions (associated cervical carotid artery occlusion). In the CS group, we provide only clinical sedation objectives based on RASS score between 0 and -3. There is no recommended drug to achieve this goal and local anaesthesia is systematically used under CS.

In conclusion, AMETIS trial is the first multicentre randomised controlled study exploring the effect of CS versus GA on functional outcome and peri-procedural complications in endovascular mechanical thrombectomy for anterior circulation AIS. The results of this study could have significant clinical and public health implications.

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AUTHOR CONTRIBUTIONS

RC, EF, SJ, LV, AF and VD are members of AMETIS trial scientific committee and contributed to the conception and design of the research protocol. RC, CFC and EF provided critical skills concerning trial interventions and procedures. CFC and RC wrote the first version of the protocol. RC wrote this manuscript. BP designed the statistical analysis plan. All other authors are involved in acquisition, analysis and interpretation of the data. All authors revised the final protocol and approved his submission.

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AMETIS trial collaborators are listed under ANARLF Network and AMETIS study group:

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COMPETING INTERESTS

RC reports personal fees from MSD and Smiths Medical France for education events, transport and accommodation fees from Novartis, Depuy France and Vasopharm outside the submitted work.

KEYWORDS

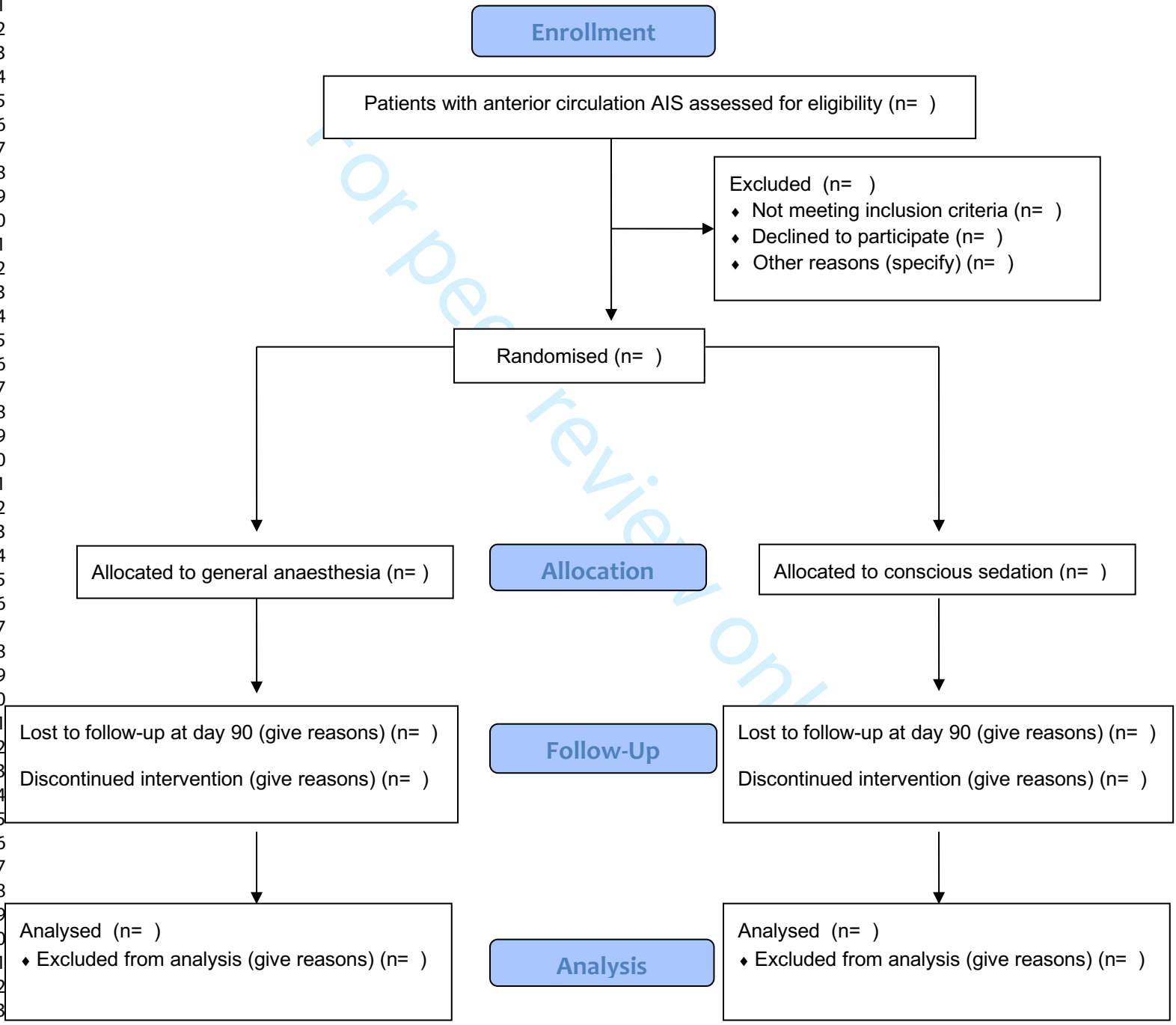
Stroke – Sedation – General Anaesthesia - Thrombectomy

WORD COUNT

3990

FIGURE LEGENDS

Figure 1: CONSORT diagram of the Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial illustrating the randomisation and flow of patients in the study. AIS: Acute Ischemic Stroke



Supplementary file 1: AMETIS trial data collection

At randomisation: Date and time of actual hospital admission, Transfer from another hospital: Y/N, Demographic data (age, height, gender and body mass index), comorbidities (hypertension: Y/N, renal failure: Y/N, cardiac failure: Y/N, diabetes mellitus: Y/N, alcohol abuse: Y/N, active smoking: Y/N), anticoagulation therapy: Y/N, antiplatelet therapy: Y/N, NIHSS score (stratification variable), premorbid mRS, brain imaging used for patient selection with corresponding ASPECT score (MRI: Y/N, AngioCT: Y/N, PerfusionCT: Y/N) [1,2], associated cervical vascular imaging: Y/N, localisation of AIS, intravenous thrombolysis (stratification variable) : Y/N, wake-up stroke: Y/N.

Intraoperative anaesthetic data: date and time of CS/GA, type (Propofol: Y/N, Thiopental: Y/N, Etomidate: Y/N, Midazolam: Y/N, Ketamine: Y/N, inhaled anaesthetics: Y/N, Sufentanil: Y/N, Remifentanil: Y/N, Succinylcholine: Y/N, Atracurium: Y/N, Cisatracurium: Y/N, Rocuronium: Y/N or others) and dose of anaesthetic drugs used, systolic, diastolic and mean arterial blood pressure every 5 minutes until 30 minutes and then every 10 minutes until the end of procedure, maximal blood pressure difference defined as maximal preintervention systolic blood pressure minus minimal perprocedural systolic blood pressure, intraprocedural maximal systolic and diastolic blood pressure, intraprocedural minimal systolic and diastolic blood pressure, pulse oxymetry every 5 minutes for 30 minutes and then every 10 minutes until the end of procedure, RASS score before arterial puncture and at the end of procedure before CS/GA removal, duration of CS or GA, volume of fluids used, type (Norepinephrine: Y/N, Ephedrine: Y/N, Phenylephrine: Y/N or others) and dose of vasoconstrictor if any, type (Nicardipine: Y/N, Urapidil: Y/N or others) and dose of antihypertensive drugs if any, intraprocedural complications (nausea: Y/N, vomiting: Y/N, aspiration: Y/N, anaphylaxis: Y/N or others), tracheal intubation

complication: Y/N, CS conversion to GA: Y/N, feasibility score estimated by the anaesthesiologist at the end of procedure.

Intraoperative neurological and radiological data: date and time of groin puncture and reperfusion if any, date and time of end of procedure (defined as the last set of radiological images), time delay between AIS symptom onset (or last time seen well for wake-up stroke) and groin puncture, time delay between AIS symptom onset and reperfusion, devices used for procedure (stent retrievers: Y/N, contact aspiration: Y/N, intra-arterial thrombolysis: Y/N, stenting: Y/N or others), number of desobstruction attempts, intervention-associated vessel complications (arterial dissection: Y/N, arterial perforation: Y/N, groin hematoma: Y/N, embolization in another arterial territory: Y/N), mTICI score at the end of procedure (ranging from 0 (no perfusion) to 3 (full perfusion with filling of all distal branches)), agitation during procedure (define as a RASS score > +1 at any moment (restless to combative patient) : Y/N), procedure difficulty associated with patient movement: Y/N, complexity of arterial catheterisation: Y/N, altered quality of images: Y/N, feasibility score estimated by the radiologist at the end of procedure.

Postoperative data at day 1 and by day 7 or hospital discharge if prior: NIHSS, groin hematoma: Y/N, pneumonia treated with antibiotics: Y/N, myocardial infarction: Y/N, acute cardiogenic pulmonary oedema: Y/N, extra pulmonary infection: Y/N, venous thromboembolism: Y/N, new event of AIS: Y/N, epilepsy: Y/N, gastrointestinal bleeding or other symptomatic bleeding: Y/N, malignant stroke evolution: Y/N, symptomatic intracranial haemorrhage: Y/N, stroke unit and hospital length of stay, unexpected intensive care unit admission: Y/N, care limitation/palliation: Y/N, mortality: Y/N, patient acceptability score.

Postoperative data at day 90: mRS score, hospital length of stay, mortality: Y/N.

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Supplementary file 2: AMETIS trial statistical analysis plan

Populations

Primary analysis will be done in modified intention to treat (ITT). Then, a per-protocol analysis will also be done to take into account protocol deviations notably crossover from CS to GA. Patients who withdraw consent will not be included in the analysis.

Intention-to treat (ITT) population: All randomised patients. This population will not be analysed in the AMETIS study.

Modified intention-to-treat population: All randomised patients except patients who:

- Withdrew consent for the use of data

  OR

- Would never have any of the intervention (CS nor GA, for example due to spontaneous or thrombolytic associated reperfusion after randomisation but before the anaesthetic procedure)

  OR

- Would have the intervention (CS or GA) without any attempt of mechanical thrombectomy due to spontaneous or thrombolytic associated reperfusion.

Per-protocol population: All randomised patients except patients having one or more major protocol violations defined as:

- Patients who would not be eligible for randomization according to inclusion/non-inclusion criteria

  OR

- Patients who accidentally would have received the wrong intervention (CS or GA)

OR

- Would never have any of the intervention (CS nor GA, for example due to spontaneous or thrombolytic associated reperfusion after randomisation but before the anaesthetic procedure)

OR

- Would have the intervention (CS or GA) without any attempt of mechanical thrombectomy due to spontaneous or thrombolytic associated reperfusion

OR

- Patients who would be withdrawn from the protocol because the patient would have withdrawn consent.

Statistical analyses

Primary analysis

Unadjusted Chi-square test (or Fisher's exact test as appropriate) for binary outcome. For rate data, the generalized linear (Stata software: command glm) model will be used with Poisson distribution (link=log and offset), including a random effect to account for centre effect. Results will be expressed as Relative Risks and 95% confidence intervals.

Secondary analyses

- For the primary outcome

Multiple logistic mixed regression will be used with the following covariates (criterion for entering variables tested in the model will be selected if P<0.10 and according to clinically relevant covariates with anticipated relationship with outcome), including stratification parameters, centre treated as a random effect. Particular attention will be paid to the study of multicollinearity.

Binary covariates

- Gender M/F
- Comorbidities Y/N
- Anticoagulation therapy Y/N
- Antiplatelet therapy Y/N
- Intravenous thrombolysis Y/N (stratification variable)
- Wake up stroke Y/N
- Quality of reperfusion: mTICI (good or bad)
- Left sided stroke Y/N
- Carotid top occlusion Y/N

Continuous covariates (with logarithmic transformation when appropriate)

- Demographic data
- Time delays

Ordinal covariates

- NIHSS score (stratification variable)
- Baseline mRS
- ASPECT score

- Localisation of AIS
- mTICI score

- For secondary outcomes

A chi-squared test (or Fisher's exact test, as appropriate) will be used for secondary binary outcomes. The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome (mRS score 0 to 2 by day 90, medical complications: intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7). Adjusted analyses will be performed with the use of random-effect Poisson generalized linear model regression and will be presented as Relative Risks and 95% confidence intervals, using the same adjustment variables.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired t test or the Mann-Whitney U test as appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Adjusted analyses, using multiple linear regression, will be conducted using the same adjustment variables and center as random-effect. Results will be expressed as regression coefficients and 95% confidence intervals.

Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure, this parameter will be treated by different ways according to literature notably as an ordinal variable. A shift analysis will be also performed with Cochrane Mantel–Haenszel for the

univariate analysis and random-effects ordinal logistic regression adjusted on initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion) for multivariable analysis.

Time-to-event curves will be calculated with the use of the Kaplan-Meier method in univariable analysis. For multivariable analysis, marginal Cox proportional hazards mode, with centre as random-effect, will be performed with results reported as hazard ratios with 95% confidence intervals, and proportional hazard assumption verified using the Schoenfeld test and plotting residuals.

Concerning the study of the parameters collected longitudinally, mixed models will be used to take into account between and within patient variability, in addition to centre random-effect. The following fixed effect will be analysed: randomisation group, time and their interaction.

Planned subgroup analyses will be done to explore potential influence of age, stroke laterality, stroke initial severity based on NIHSS, time delay, thrombus location and associated extracranial carotid artery stenosis/thrombosis on the incidence of the primary outcome. The study of interaction between randomization group and subgroup will be analysed.

If missing data are greater than 5%, an additional analysis will be performed using the multiple imputation method (Stata software, command mi).

A two-sided P value of less than 0.05 will be considered for statistical significance.

As proposed by some statisticians,[1,2] a particular focus will be given to the magnitude of differences, in addition to inferential statistical tests expressed using p-values.

Outcomes

Primary outcome measure: The primary outcome measure is a composite of functional independence at 3 months and absence of medical complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Medical complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary outcome measures:

- Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure[3,4]:
  - Ordinal score on the mRS by day 90
  - Functional independence by day 90 defined as a mRS score 0-2
  - Excellent recovery by day 90 defined as a mRS score 0-1
  - Moderate recovery by day 90 defined as a mRS score 0-3
  - Shift analysis of day 90 mRS adjusted for initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion)
  - Good recovery defined with sliding dichotomy responder analysis relating day 90 mRS with baseline NIHSS score: mRS 0 for NIHSS ≤ 7; mRS 0-1 for NIHSS 8-14; mRS 0-2 for NIHSS > 14
- Intraprocedural hemodynamic and ventilatory conditions and complications defined as hypotension, blood pressure variability, hypoxemia and aspiration
- Intervention-associated vessel and others complications defined as arterial dissection or perforation, groin hematoma, embolization in another arterial territory

- Door to groin puncture delay
- Door to reperfusion delay
- Successful reperfusion defined by the modified Treatment In Cerebral Ischemia (mTICI) reperfusion scale of 2b or 3 (with a grade of 2b or 3 indicating reperfusion of > 50% of the affected territory)
- NIHSS by day 1 and day 7
- Stroke unit and hospital length of stay
- Medical complications by day 7 defined as pneumonia, acute cardiogenic pulmonary oedema, myocardial infarction, extra pulmonary infection, venous thromboembolism, new event of AIS, epilepsy, gastrointestinal bleeding or other symptomatic bleeding
- Malignant stroke evolution by day 7
- Symptomatic intracranial haemorrhage by day 7 defined as brain haemorrhage on imaging associated with an increase of at least 4 points in the NIHSS score
- Unexpected intensive care unit admission by day 7
- Mortality by day 7 and day 90
- Procedural feasibility score estimated by the radiologist and the anaesthesiologist and patient acceptability score

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5 and 19
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	19
Protocol version	#3	Date and version identifier	13
Funding	#4	Sources and types of financial, material, and other support	See note 1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 and 2

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	See note 2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See note 3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15 and 19
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7 and 8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7 and 8
Objectives	#7	Specific objectives or hypotheses	8 and 9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10 and 11

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11 and 18
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10 and 11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	See note 4
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14, 15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	See note 5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	See note 6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	See note 7
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18 and 19

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	26 and 27
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases,	20 and 21

		or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Author notes

1. 20, 26 and 27
2. 1, 2 and 20
3. 20, 25, 26, 27 and
4. 11, 12 and 13
5. 16, 17 and supplementary file
6. 17 and supplementary file
7. 18 and supplementary file

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Sedation versus general anaesthesia in endovascular therapy for anterior circulation acute ischemic stroke: the multicentre randomised controlled AMETIS trial study protocol

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Sedation versus general anaesthesia in endovascular therapy for anterior circulation acute ischemic stroke: the multicentre randomised controlled AMETIS trial study protocol

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ABSTRACT

Introduction: Endovascular thrombectomy is the standard of care for anterior circulation acute ischemic stroke (AIS) secondary to emergent large vessel occlusion in patients who qualify. General Anaesthesia (GA) or Conscious Sedation (CS) are usually required to ensure patient comfort and avoid agitation and movement during thrombectomy. However, the question of whether the use of GA or CS might influence functional outcome remains debated. Indeed, conflicting results exist between observational studies with better outcomes associated with CS and small monocentric randomized controlled trials favouring GA. Therefore, we aim to evaluate the effect of CS versus GA on functional outcome and peri-procedural complications in endovascular mechanical thrombectomy for anterior circulation AIS.

Methods and analysis: Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is an investigator initiated, multicentre, prospective, randomised controlled, two-arm trial. AMETIS trial will randomised 270 patients with anterior circulation AIS in a 1:1 ratio, stratified by centre, NIHSS (≤ 15 or > 15) and association of intravenous thrombolysis or not to receive either CS or GA. The primary outcome is a composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or cardiogenic acute pulmonary oedema or malignant stroke evolution occurring by day 7.

Ethics and dissemination: The AMETIS trial was approved by an independent ethics committee. Study began in august 2017. Results will be published in an international peer-reviewed medical journal.

Trial registration number: NCT03229148.

(Abstract word count: 265)

ARTICLE SUMMARY

Strengths and limitations of this study

- Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is the first multicentre randomised controlled trial comparing conscious sedation (CS) and general anaesthesia (GA) in thrombectomy for anterior circulation (internal carotid artery and/or proximal middle cerebral artery) acute ischemic stroke.
- The multicentre setting and large pragmatic inclusions criteria compatible with current practice and recommendations will allow external validity.
- Stratification based on centre, stroke severity and concomitant administration of intravenous thrombolysis will allow groups homogeneity and comparability.
- Composite primary outcome measure will allow evaluation of functional independence at 3 months and neurological and non-neurological peri-procedural complications. Secondary outcomes will measure different important aspects of care.
- Despite the absence of specific anaesthetic protocol concerning CS and GA management in order to reinforce external validity, perfusion pressure determinants (arterial blood pressure and carbon dioxide tension) will have to be maintained in strict limits.

INTRODUCTION

Background and rationale

Endovascular mechanical thrombectomy dramatically changed management of acute ischemic stroke (AIS). Randomised controlled trials demonstrated improved outcome associated with the procedure using stent-retrievers in anterior circulation AIS.[1-6] The American Heart Association/American Stroke Association, as others national medical societies, rapidly endorsed this strategy as a level 1 recommendation in association if possible with intravenous thrombolysis.[7] Nevertheless, peri-procedural management in the field added complexity since immobility and cardio-respiratory stability could be incompatible with acute neurological failure in these frail patients. Notably, the optimal management strategy during thrombectomy, using either General Anaesthesia (GA) or Conscious Sedation (CS), remains controversial. It was traditionally assumed that CS was superior since GA could negatively affect brain physiology especially cerebral blood flow (CBF) in the penumbra area related to induced systemic hypotension and carbon dioxide modulation.[8] Also, it was stressed the possible excessive delay associated with GA initiation that counteract a "time is brain" strategy. Nevertheless, evidence based medicine supporting this concept is scarce with methodological issues associated with observational data.[9] Notably, sickest patients were prone to receive GA and the anaesthetic strategy was not protocolized nor randomised.[10] We could conceptually argue possible benefits of GA providing systemic hypotension is treated and avoided: 1) immobility that could facilitate an easier, rapid and effective technical procedure, 2) airway protection since AIS patients are prone to aspiration pneumonia related to neurological injury, 3) patient comfort in a highly stressful environment with sometimes prolonged procedures.[9] Recently, 3 small monocentric randomised controlled trials specifically addressed effect of anaesthesia care on stroke outcome. First, the SIESTA trial randomised 150 patients between CS and GA.[11] No difference occurred in the National Institutes of Health Stroke Scale (NIHSS)

at 24 hours, which was the primary outcome. More patients were functionally independent after 3 months, defined as a Modified Rankin Scale (mRS, which ranges from 0 [no symptom] to 6 [death]) score 0 to 2, in the GA group. Second, the AnStroke trial randomised 90 patients between CS and GA.[12] No difference was achieved concerning the primary outcome mRS at 3 months and others secondary outcomes. Finally, the GOLIATH trial randomised 128 patients between CS and GA.[13] There was no difference in the volume of infarct growth as a primary outcome despite significantly higher successful reperfusion and better mRS score at 3 months in the GA group. On the assumption of these discrepancies, a multicentre randomised controlled trial comparing CS and GA is urgently needed.[14,15]

Objectives

Primary objective

The primary objective of the study is to determine whether CS or GA is associated with improved outcome defined as a composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or cardiogenic acute pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary objectives

The study will also explore if CS or GA in endovascular therapy for anterior circulation AIS is associated with difference in several outcomes: functional independence by day 90, intraprocedural hemodynamic and ventilatory conditions, intervention-associated vessel and others complications, procedural time delays, successful recanalization, stroke unit and hospital

length of stay, perioperative complications by day 7, unexpected intensive care unit admission by day 7, mortality by day 7 and day 90.

Trial design

The Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is an investigator initiated, national, multicentre, prospective, open-labelled, stratified, randomised controlled two-arm trial.

Consort diagram

Figure 1 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram of the AMETIS trial.[16]

METHODS AND ANALYSIS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

This manuscript was written in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.[17]

Study setting

The AMETIS trial takes place in 11 university hospitals in France (Clermont-Ferrand, Paris Pitié-Salpêtrière, Paris Saint-Antoine, Lyon, Toulouse, Marseille, Montpellier, Rouen, Lille, Poitiers and Saint-Etienne).

Eligibility criteria

Inclusion criteria

Adult patients admitted for anterior circulation (internal carotid artery and/or proximal middle cerebral artery) AIS, eligible for thrombectomy as decided by the neurology/neuroradiology teams based on current guidelines using brain imaging selection.[15]

Exclusion criteria

Patients with one or more criteria are not included:

- Age < 18 years.
- Coma or altered vigilance defined as a score ≥ 2 on the level of consciousness 1A subscale of the NIHSS.[18]
- Premorbid loss of autonomy defined as a mRS > 1.[19]
- Posterior circulation stroke.
- Associated cerebral haemorrhage.
- Stroke complicating another acute illness or postoperative stroke.
- Pregnant or breastfeeding women.
- Adult under the protection of the law.

Interventions

Patients eligible for inclusion will be randomly assigned to CS or GA after a routine medical anaesthetic emergency evaluation has been made by a certified senior Anaesthesiologist. As required by French law, all contraindications and/or known allergy to anaesthetics will be registered.

Modality of the CS and GA protocols are left to the attending anaesthesiologist in accordance with current and local guidelines providing systolic blood pressure is maintained between 140 and 180 mmHg (with vasopressor infusion if necessary) and arterial pulse oxymetry (SpO2) > 94 %.[15]

Under GA, tracheal intubation is mandated and mechanical ventilation should be managed to maintain an End Tidal CO2 (EtCO2) level between 30 and 35 mmHg.

Under CS, a minimal to moderate sedation level has to be targeted as defined by the American Society of Anesthesiologists (ASA) recommendations.[20] Clinical sedation level will be evaluated using the Richmond Agitation Sedation Scale (RASS) with an objective between 0 and -3 (defined as a patient alert and calm or drowsy with sustained awakening (eye opening/eye contact) to voice ≥ 10 seconds or briefly awake to voice with eye contact < 10 seconds or movement/eye opening to voice).[21,22] Effective spontaneous ventilation has to be maintained.

In the CS group, a crossover to GA with tracheal intubation is recommended in case of severe agitation, coma defined as a -4 or -5 RASS value (no response to voice but movement or eye opening to physical stimulation or no response to physical stimulation) despite stopping sedative drugs, loss of airway protective reflexes, respiratory failure and incoercible vomiting.

Stent retrievers are the preferred devices to perform thrombectomy. Nevertheless, alternative devices could be used.

At the end of intervention, GA and CS have to be immediately stopped and in the GA group extubation should occur as soon as possible.

After the intervention, depending on each hospital organization and anaesthesia modality (GA or CS), patients are transferred to the post anaesthesia care unit or neurological or general intensive care unit.

Outcomes

Primary outcome measure

The primary outcome measure is a composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary outcome measures

- mRS by day 90[19,23,24]
    - Ordinal score on the mRS by day 90
    - Functional independence by day 90 defined as a mRS score 0-2
    - Excellent recovery by day 90 defined as a mRS score 0-1
    - Moderate recovery by day 90 defined as a mRS score 0-3
    - Shift analysis of day 90 mRS adjusted for initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion)
    - Good recovery defined with sliding dichotomy responder analysis relating day 90 mRS with baseline NIHSS score: mRS 0 for NIHSS ≤ 7; mRS 0-1 for NIHSS 8-14; mRS 0-2 for NIHSS > 14
- Intraprocedural hemodynamic and ventilatory conditions and complications defined as hypotension, blood pressure variability, hypoxemia and aspiration
- Intervention-associated vessel and others complications defined as arterial dissection or perforation, groin hematoma, embolization in another arterial territory
- Stroke onset to door delay, door to groin puncture delay, door to reperfusion delay, stroke onset to groin puncture delay, GA/CS induction to groin puncture delay, duration of the procedure, stroke onset to reperfusion delay (see supplementary file 1 for definitions).

- Successful reperfusion defined by the modified Treatment In Cerebral Ischemia (mTICI) reperfusion scale of 2b or 3 (with a grade of 2b or 3 indicating reperfusion of > 50% of the affected territory)[25]
- NIHSS by day 1 and day 7[18]
- Stroke unit and hospital length of stay
- Perioperative complications by day 7 defined as pneumonia, acute cardiogenic pulmonary oedema, myocardial infarction, extra pulmonary infection, venous thromboembolism, new event of AIS, epilepsy, gastrointestinal bleeding or other symptomatic bleeding[26]
- Malignant stroke evolution by day 7[27]
- Symptomatic intracranial haemorrhage by day 7 defined as brain haemorrhage on imaging associated with an increase of at least 4 points in the NIHSS score[28]
- Unexpected intensive care unit admission by day 7
- Mortality by day 7 and day 90
- Procedural feasibility score estimated by the radiologist and the anaesthesiologist and patient acceptability score[29]

Recruitment

Patients are expected to be included during a 2-year period starting in august 2017.

2016-2017: Protocol, approvals from ethics committee (*CPP Sud-Est I*) and the French Medicine Agency (*Agence Nationale de Sécurité du Médicament et des produits de santé, ANSM*); trial tool development (online case report form and randomisation system).

2017-2019: Inclusion of patients.

2019: cleaning and closure of the database, data analyses, writing of the manuscript and submission for publication.

Trial status

The current protocol is version 4.0. Study started enrolment in august 2017. To date (28th October 2018), 186 patients have been randomised in the study.

Patient and public involvement

Patients will not be invited to comment on study design or conduction of the trial.

METHODS: ASSIGNEMENT OF INTERVENTIONS

Allocation and sequence generation

Randomisation will be conducted over a dedicated password-protected, SSL-encrypted website (CSOnline, Clinsight) to allow concealed allocation. Each patient will be given a unique patient number and randomisation number. The allocation sequence will be generated with the use of a minimisation algorithm stratified according to centre, NIHSS score (≤ 15 or > 15) and association of intravenous thrombolysis or not. The participant allocation will be carried out by local investigators who will log into the randomisation system using a personal ID and will enter any relevant information.

Blinding

This is an open label, unblinded trial for the patient and the physician in charge, related to the nature of the intervention (GA with endotracheal intubation or CS). Assessor blinded evaluation of the primary outcome will be performed since the assessor and statistician will be masked to the subjects' assignment group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

At each participating centre, data will be collected and entered into the web-based electronic case report form (eCRF) (CSOnline, Clinsight) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators. From the eCRF, the trial database will be created. Paper case report form will be used in case of technical problems with the eCRF. Trained research coordinators will monitor data collection. Data collected are presented in supplementary file 1.

Patient withdrawal:

Evaluated procedure is tested during endovascular thrombectomy. Nevertheless, participant can withdraw consent at any time without need for further explanation. Data will be destroyed and a new patient will be randomised for the complete sample size.

Statistical methods

Sample size estimation

According to literature analysis based on 5 international randomised controlled trials about endovascular thrombectomy in anterior circulation AIS, frequency of events constitutive of the composite primary outcome was expected at 50%.[1-5] Then, we postulated that 124 patients per group would provide 90% statistical power to detect an absolute between-group difference equals 20% (50% vs. 30%) for a two-sided type I error at 5%. Assuming lost to follow-up and modified intention to treat population requirements (as defined in supplementary file 2) between 5% and 10%, 270 patients have to be recruited for the study.

Interim analysis

A safety interim analysis is planned after 50% of inclusions. The independent Data and Safety Monitoring Board (DSMB) could recommend stopping the study if prolongation of the trial clearly compromises patient safety (in case of serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs)). The steering committee (SC) will be responsible to continue, hold or stop the study based on the DSMB recommendations.

Statistical analysis

A predefined statistical analysis plan will be followed (supplementary file 2). All analyses will be conducted with Stata software (version 13, StataCorp, College Station, USA) and R (http://cran.r-project.org/) before the breaking of randomisation code, in line with the International Conference on Harmonization Good Clinical Practice guidelines. A two-sided p value of less than 0.05 will be considered for statistical significance.

Primary analysis will be done in modified intention to treat (mITT). Then, a per-protocol analysis will also be done to take into account protocol deviations notably crossover from CS to GA. Patients who withdraw consent will not be included in these analyses.

Continuous variables will be presented as mean and standard-deviation or as median and quartiles otherwise. Normality will be assessed using the Shapiro-Wilk test and homoscedasticity will be assessed using the Fisher-Snedecor test.

Concerning the comparison of the primary composite outcome between CS and GA, a Chi2 test or a Fischer's exact test will be performed as appropriate. Adjusted analysis will be conducted with the use of robust random-effects Poisson generalised linear regression will be used (1) to take into account adjustment on possible confounding covariates selected according to clinical relevance and stratification variables (including stratification parameters) and (2) to consider within and between centre variability (as random-effect). The results will be presented as relative risks and 95% confidence interval (CIs). The Hochberg procedure will be used to adjust

for multiple testing of components of the composite primary outcome.

Concerning the comparisons of secondary outcomes between groups, Student t test or non-parametric Mann-Whitney test as appropriate will be used for quantitative parameters such as intraoperative blood pressure, oxygen saturation, timing delays or length of stays. Chi-squared test or Fischer's exact test will be used for categorical parameters such as NIHSS and ordinal and nominal (dichotomized) mRS, intervention-associated and perioperative complications, mTICI score, functional independence at day 90 and mortality. Results will be reported as effect-sizes and absolute differences with 95% CIs. Then, **multiple regression** will be conducted using random-effects models taking into account between and within centre variability: linear mixed models for quantitative endpoints and generalized linear mixed regression for categorical endpoints. The results will be expressed, respectively, as regression coefficients and relative risks, with 95% CIs.

Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure, this parameter will be treated by different ways according to literature notably as an ordinal variable.[15,30] A shift analysis will also be performed: Cochrane Mantel–Haenszel for the univariate analysis and random-effects ordinal logistic regression adjusted on initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion) for **multiple regression**.

Time-to-event curves will be calculated with the use of the Kaplan-Meier method in univariable analysis. For **multiple regression**, marginal Cox proportional hazards model (with centre as random effect) will be performed. Proportional hazard assumption will be verified using the Schoenfeld test and plotting residuals. Results will be reported as HRs with 95% CIs.

Concerning the study of parameters collected longitudinally (in particular NIHSS score at day 1 and day 7, arterial pressure and arterial oxygen saturation), mixed models will be used to take into account between and within patient variability, in addition to centre random-effect. The following fixed effect will be analysed: randomisation group, time and their interaction (time x

group).

According to clinical relevance and to European Medicines Agency (EMA) and Consolidated Standards of Reporting Trials (CONSORT) recommendations, post-hoc analyses will be proposed after the study of subgroup × randomisation group interaction in regression models (for repeated data or not).

Missing values will be notified and analysed. A sensitivity analysis will be performed and the nature of missing data will be studied (missing at random or not). If the frequency is > 5%, additional analyses will be performed using the multiple imputation method. [31]

METHODS: MONITORING

Data monitoring

Before the start of the study, anaesthetic, neurological and radiological medical and paramedical teams are trained at each site for the study protocol by study coordinators. Physicians are in charge of patient screening and inclusion. Patients admitted for stroke treated by endovascular mechanical thrombectomy and not included in the study will be recorded anonymously at each centre into a screening log. Data will be collected in a web-based eCRF by trial personnel. Each centre will only have access to site-specific data. Each patient will receive a unique trial identification number. Only the investigators and research team will have access to any protected health information of study participants and any study data.

Data monitoring and quality control will be conducted in each centre after the first 10 inclusions then after the next 20 inclusions and at the end of the study by official representatives of the study promoter (Department of Clinical Research and Innovation, Clermont-Ferrand University Hospital).

Data will be handled according to the French law. All originals records (including consent forms, reports of SUSARs and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years. Only the principal investigators and the statistician will have access to the final dataset.

Harms

Every adverse events that could be related to the trial will be reported to the trial coordinating centre. According to the French law, all suspected serious adverse events will be reported to the ANSM. The DSMB will also be informed. DSMB is independent from the trial investigators and will perform an ongoing review of safety parameters and study conduct. DSMB members are 2 independent physicians in Anaesthesia / Critical Care Medicine and Neurology, and a Biostatician that have skills and expertise in Anaesthesia, clinical Neuroscience and clinical research. The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety of the interventions during the trial and for monitoring the overall conduct of the trial. DSMB could also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. No formal criteria are set to stop the study. However, recommendations for pausing or stopping the study could be made by DSMB in case of SARs and SUSAR. The scientific committee will be responsible for promptly reviewing the DSMB recommendations and to decide whether to continue, hold or stop the study, and to determine whether amendments to the protocol are needed.

ETHICS AND DISSEMINATION

Research ethics approval

The AMETIS study is conducted in accordance with the Declaration of Helsinki and was registered at http://www.clinicaltrial.gov on 25 July 2017 and last updated on 5 September 2017

with trial identification number NCT03229148. The trial was approved by the ethics committee *CPP Sud-Est I* on 22 May 2017 (approval number 2017-11) and ANSM on 6 march 2017 (approval number 2016-A02064-47). Any change to eligibility criteria, outcomes and analyses will be communicated to investigators, the ethics committee and the ANSM to obtain their approval.

Consent or assent

Whenever possible to include the patient, written inform consent will be searched. Nevertheless, related to neurological injury and emergency, the patient may be unable to provide written informed consent. In this case, written informed consent could be obtained from the patient next of kin if immediately available. Otherwise, an emergency consent procedure is used with investigator signature countersigned by an independent physician. As soon as possible after recovery, written informed consent from the patient will be searched to continue the study. This consent strategy was approved by the Institutional Review Board and the ethics committee *CPP Sud-Est I* on 22 May 2017 in accordance with the 2013 Declaration of Helsinki.

Funding

The study is an investigator-initiated trial with study promotion performed by Clermont-Ferrand university hospital, Clermont-Ferrand, France. There is no industry support or involvement in the trial. This study is supported by grants from the French Ministry of Health (Projet Hospitalier de Recherche Clinique Interrégional 2016). The funders have no influence on study protocol, conduct and results analysis.

Dissemination policy

On study completion, manuscript will be submitted to one peer-reviewed journal regardless of the results. All trial sites will be acknowledged and every investigators name will appear under

"AMETIS trial group" in the final manuscript. AMETIS study scientific committee will grant authorship depending on personal input according to the Vancouver guidelines. If a trial site investigator is to gain authorship, the site has to include 30 patients or more. If the site includes 50 patients or more, two authorships will be granted. A writing committee will be composed of members of the scientific committee and investigators to define the order of authors of any publications. Trial results will also be presented at local, national and international meetings.

DISCUSSION

We recently observed the "thrombectomy revolution" in anterior circulation AIS.[32] Emergency interventional procedures in frail stroke patients often require skills from Anaesthesia providers since immobility is needed and severe intra-procedural complications may occur (for example coma, agitation or aspiration pneumonia).

Taking into account the increasing volume of procedures and the potential effect of the anaesthetic strategy on outcome with discrepancy in literature, it appears essential to provide a multicentre randomised controlled trial to enhance external validity as suggested by recent recommandations.[15]

Concurrent ongoing trials with day 90 mRS as a primary outcome are planning to recruit 635 patients to demonstrate non-inferiority between CS and GA,[33] 350 patients to demonstrate superiority of CS vs GS (NCT02822144) or 260 patients to demonstrate superiority of GA vs CS (NCT03263117).

Some limitations could be opposed to the AMETIS trial protocol. First, no specific anaesthetic protocol will be used. We choose this strategy in a pragmatic way since no data demonstrate that a drug is better than another even if modulation of CBF could be variable. However, the protocol requires strict objectives for systolic blood pressure and "normal" blood carbon dioxide tension in GA group.[34,35] Drugs and dose will be monitored. Second, no maximal time

delay from stroke onset or maximal/minimal NIHSS values are recommended in order to adhere to a pragmatic investigator-based approach. This strategy complies with recent trials and recommendations: patient selection for thrombectomy is made on angioCT or MRI scans with eventual mismatch evaluation especially when delay is > 6 hours and for wake-up strokes.[15,36,37] Delays and imaging modality used for selection will be monitored. Notably, despite published trials mentioned NIHSS limits as inclusion/exclusion criteria, providing thrombectomy is indicated based on actual recommendations, the optimal anaesthetic strategy deserves evaluation whatever the NIHSS is. Stratification on NIHSS score with a cut-off of 15 will provide homogeneous groups in term of initial severity. As recommended, outcome measures will include adjustments for baseline severity.[15] Third, despite thrombectomy might benefit to patients with premorbid mRS>1, we excluded these patients since evaluation is difficult in emergency condition and inclusion of dependent patients could strongly affect the primary outcome. This strategy was adopted by others.[3-5,37] Fourth, we choose a composite principal outcome measure since anaesthesia strategy could affect functional independence at 3 months but also peri-interventional morbidity. The effect size that we could expect on functional independence at 3 months is probably far less than thrombectomy on its own. Based on actual literature, SIESTA trial found dramatically decreased functional independence associated with CS with only 18% of mRS 0-2 compared to 37% in GA.[11] 18% of patients being independent is far less than in thrombectomy trials where it barely represents controlled groups (intravenous thrombolysis alone).[1-6] With these proportions, 240 patients would have been necessary to demonstrate a statistical difference with a beta power of 90% but we could expect important centre effect in SIESTA trial. On the contrary, ANSTROKE trial didn't find any difference between groups, with functional independence in respectively 42 and 40% of patients between GA and CS.[12] Based on these 2 trials, functional independence could be obtained in roughly 40% of patients under GA. Providing a 20% variation in positive or negative effect on

functional independence, more than 1000 patients would be required with a 80% beta power. An anaesthesia size effect of more than 20% appeared unrealistic.

Fifth, even if possible in selected patients, we will not study local anaesthesia alone. Management solely under local anaesthesia is difficult regarding comfort and immobility particularly in sickest patients, in left hemisphere strokes with aphasia and in tandem lesions (associated cervical carotid artery occlusion). In the CS group, we provide only clinical sedation objectives based on RASS score between 0 and -3. There is no recommended drug to achieve this goal and local anaesthesia is systematically used under CS.

In conclusion, AMETIS trial is the first multicentre randomised controlled study exploring the effect of CS versus GA on functional outcome and peri-procedural complications in endovascular mechanical thrombectomy for anterior circulation AIS. The results of this study could have significant clinical and public health implications.

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AUTHOR CONTRIBUTIONS

RC, EF, SJ, LV, AF and VD are members of AMETIS trial scientific committee and contributed to the conception and design of the research protocol. RC, CFC and EF provided critical skills concerning trial interventions and procedures. CFC and RC wrote the first version of the protocol. RC wrote this manuscript. BP designed the statistical analysis plan. SM, ACL, PFP, SM, BT, CDF, FV, EC, AM, MB, EC and JEB are involved in acquisition, analysis and interpretation of the data. All authors revised the final protocol and approved his submission.

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COMPETING INTERESTS

RC reports personal fees from MSD and Smiths Medical France for education events, transport and accommodation fees from Novartis, Depuy France and Vasopharm outside the submitted work.

KEYWORDS

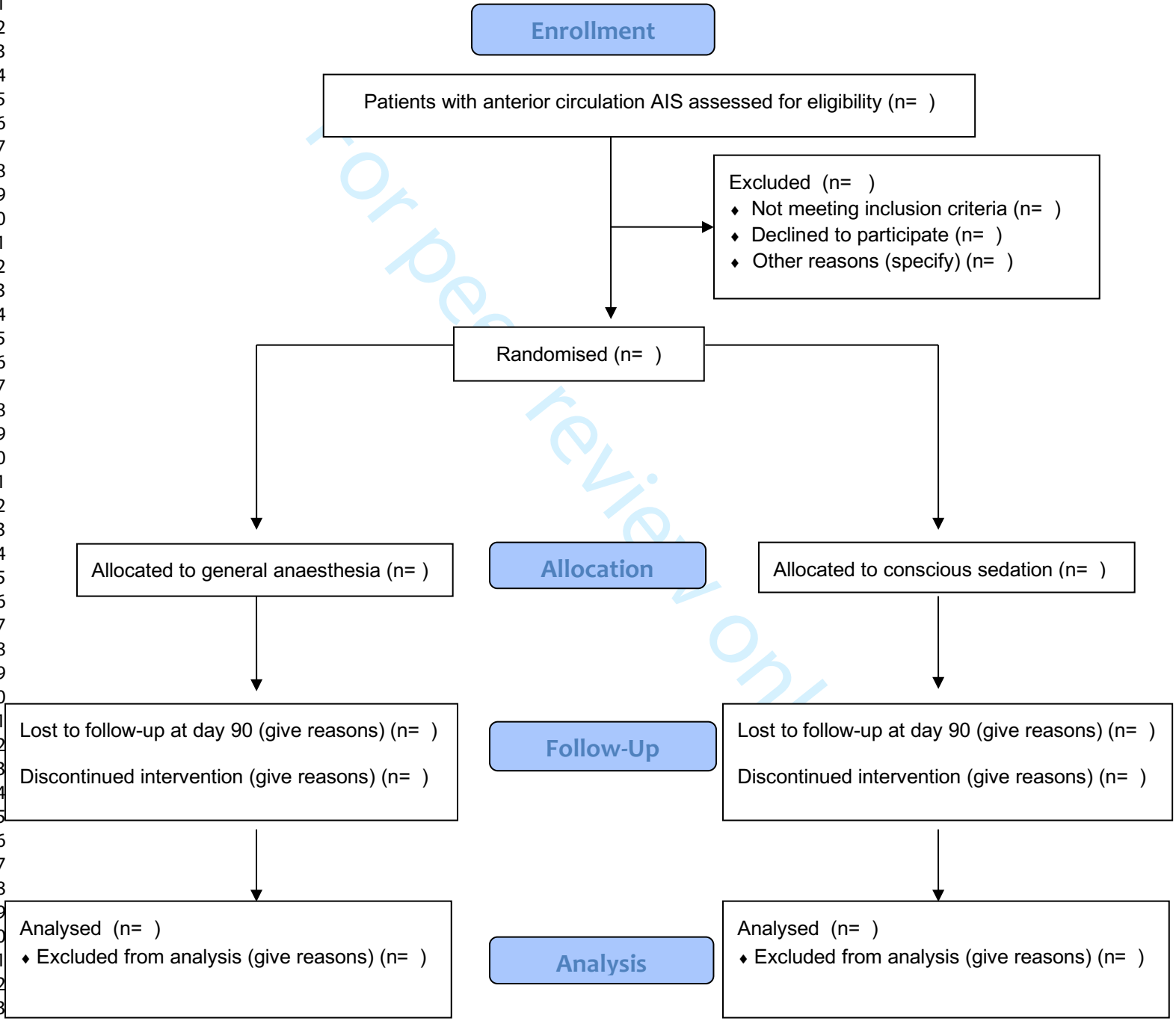
Stroke – Sedation – General Anaesthesia - Thrombectomy

WORD COUNT

3990

FIGURE LEGENDS

Figure 1: CONSORT diagram of the Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial illustrating the randomisation and flow of patients in the study. AIS: Acute Ischemic Stroke



Supplementary file 1: AMETIS trial data collection

At randomisation: Date and time of actual hospital admission, Transfer from another hospital: Y/N, Demographic data (age, height, gender and body mass index), comorbidities (hypertension: Y/N, renal failure: Y/N, cardiac failure: Y/N, diabetes mellitus: Y/N, alcohol abuse: Y/N, active smoking: Y/N, chronic obstructive pulmonary disease: Y/N), ongoing respiratory infection: Y/N, anticoagulation therapy: Y/N, antiplatelet therapy: Y/N, NIHSS score (stratification variable), premorbid mRS, brain imaging used for patient selection with corresponding ASPECT score (MRI: Y/N, AngioCT: Y/N, PerfusionCT: Y/N)[1,2], associated cervical vascular imaging: Y/N, localisation of AIS, intravenous thrombolysis (stratification variable) : Y/N, wake-up stroke: Y/N.

Intraoperative anaesthetic data: date and time of CS/GA, type (Propofol: Y/N, Thiopental: Y/N, Etomidate: Y/N, Midazolam: Y/N, Ketamine: Y/N, inhaled anaesthetics: Y/N, Sufentanil: Y/N, Remifentanil: Y/N, Succinylcholine: Y/N, Atracurium: Y/N, Cisatracurium: Y/N, Rocuronium: Y/N or others) and dose of anaesthetic drugs used, systolic, diastolic and mean arterial blood pressure every 5 minutes until 30 minutes and then every 10 minutes until the end of procedure, hypotension:Y/N (defined as one episode of systolic blood pressure < 120 mmHg during the prespecified time points of blood pressure measurement),[3] maximal blood pressure difference defined as maximal preintervention systolic blood pressure minus minimal perprocedural systolic blood pressure, intraprocedural maximal systolic and diastolic blood pressure, intraprocedural minimal systolic and diastolic blood pressure, pulse oxymetry every 5 minutes for 30 minutes and then every 10 minutes until the end of procedure, RASS score before arterial puncture and at the end of procedure before CS/GA removal, duration of CS or GA, volume of fluids used, type (Norepinephrine: Y/N, Ephedrine: Y/N, Phenylephrine: Y/N or others) and dose of vasoconstrictor if any, type (Nicardipine: Y/N, Urapidil: Y/N or others) and dose of antihypertensive drugs if any, intraprocedural complications (nausea: Y/N,

vomiting: Y/N, aspiration: Y/N, anaphylaxis: Y/N or others), tracheal intubation complication: Y/N, CS conversion to GA: Y/N, feasibility score estimated by the anaesthesiologist at the end of procedure.

Intraoperative neurological and radiological data: date and time of groin puncture and reperfusion if any, date and time of end of procedure (defined as the last set of radiological images), devices used for procedure (stent retrievers: Y/N, contact aspiration: Y/N, intra-arterial thrombolysis: Y/N, stenting: Y/N or others), number of desobstruction attempts, intervention-associated vessel complications (arterial dissection: Y/N, arterial perforation: Y/N, groin hematoma: Y/N, embolization in another arterial territory: Y/N), mTICI score at the end of procedure (ranging from 0 (no perfusion) to 3 (full perfusion with filling of all distal branches)), agitation during procedure (define as a RASS score > +1 at any moment (restless to combative patient) : Y/N), procedure difficulty associated with patient movement: Y/N, complexity of arterial catheterisation: Y/N, altered quality of images: Y/N, feasibility score estimated by the radiologist at the end of procedure.

Procedural time delays: Stroke onset to door delay is time from stroke symptom (or last time seen well for wake-up strokes) to actual hospital admission, Door to groin puncture delay is time from actual hospital admission to groin puncture, Stroke onset to groin puncture delay is time from stroke symptom (or last time seen well for wake-up strokes) to groin puncture, Door to reperfusion delay is time from actual hospital admission to reperfusion, GA/CS induction to groin puncture delay is time from administration of the first anaesthetic/sedative agent to groin puncture, Duration of the procedure is time from groin puncture to end of procedure (defined as the last set of radiological images), Stroke onset to reperfusion delay is time from stroke symptom (or last time seen well for wake-up strokes) to reperfusion (if any).

Postoperative data at day 1 and by day 7 or hospital discharge if prior: NIHSS, groin hematoma: Y/N, pneumonia treated with antibiotics: Y/N, myocardial infarction: Y/N, acute

cardiogenic pulmonary oedema (defined as evidence of fluid accumulation in the alveoli due to poor cardiac function)[4]: Y/N, extra pulmonary infection: Y/N, venous thromboembolism: Y/N, new event of AIS: Y/N, epilepsy: Y/N, gastrointestinal bleeding or other symptomatic bleeding: Y/N, malignant stroke evolution: Y/N, symptomatic intracranial haemorrhage: Y/N, stroke unit and hospital length of stay, unexpected intensive care unit admission: Y/N, care limitation/palliation: Y/N, mortality: Y/N, patient acceptability score.

Postoperative data at day 90: mRS score, hospital length of stay, mortality: Y/N.

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Supplementary file 2: AMETIS trial statistical analysis plan

Populations

Primary analysis will be done in modified intention to treat (ITT). Then, a per-protocol analysis will also be done to take into account protocol deviations notably crossover from CS to GA. Patients who withdraw consent will not be included in the analysis.

Intention-to treat (ITT) population: All randomised patients. This population will not be analysed in the AMETIS study.

Modified intention-to-treat population: All randomised patients except patients who:

- Withdrew consent for the use of data

  OR

- Would never have any of the intervention (CS nor GA, for example due to spontaneous or thrombolytic associated reperfusion after randomisation but before the anaesthetic procedure)

  OR

- Would have the intervention (CS or GA) without any attempt of mechanical thrombectomy due to spontaneous or thrombolytic associated reperfusion.

Per-protocol population: All randomised patients except patients having one or more major protocol violations defined as:

- Patients who would not be eligible for randomization according to inclusion/non-inclusion criteria

  OR

- Patients who accidentally would have received the wrong intervention (CS or GA)

  OR

- Would never have any of the intervention (CS nor GA, for example due to spontaneous or thrombolytic associated reperfusion after randomisation but before the anaesthetic procedure)

  OR

- Would have the intervention (CS or GA) without any attempt of mechanical thrombectomy due to spontaneous or thrombolytic associated reperfusion

  OR

- Patients who would be withdrawn from the protocol because the patient would have withdrawn consent.

Statistical analyses

Primary analysis

Unadjusted Chi-square test (or Fisher's exact test as appropriate) for binary outcome. For rate data, the generalized linear (Stata software: command glm) model will be used with Poisson distribution (link=log and offset), including a random effect to account for centre effect. Results will be expressed as Relative Risks and 95% confidence intervals.

Secondary analyses

- For the primary outcome

Multiple logistic mixed regression will be used with the following covariates (criterion for entering variables tested in the model will be selected if $P<0.10$ and according to clinically relevant covariates with anticipated relationship with outcome), including stratification

parameters, centre treated as a random effect. Particular attention will be paid to the study of multicollinearity.

Binary covariates

- Gender M/F
- Comorbidities Y/N
- Anticoagulation therapy Y/N
- Antiplatelet therapy Y/N
- Intravenous thrombolysis Y/N (stratification variable)
- Wake up stroke Y/N
- Quality of reperfusion: mTICI (good or bad)
- Left sided stroke Y/N
- Carotid top occlusion Y/N

Continuous covariates (with logarithmic transformation when appropriate)

- Demographic data
- Time delays

Ordinal covariates

- NIHSS score (stratification variable)
- Baseline mRS
- ASPECT score
- Localisation of AIS
- mTICI score

- For secondary outcomes

A chi-squared test (or Fisher's exact test, as appropriate) will be used for secondary binary outcomes. The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome (mRS score 0 to 2 by day 90, perioperative complications: intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7). Adjusted analyses will be performed with the use of random-effect Poisson generalized linear model regression and will be presented as Relative Risks and 95% confidence intervals, using the same adjustment variables.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired t test or the Mann-Whitney U test as appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Adjusted analyses, using multiple linear regression, will be conducted using the same adjustment variables and center as random-effect. Results will be expressed as regression coefficients and 95% confidence intervals.

Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure, this parameter will be treated by different ways according to literature notably as an ordinal variable. A shift analysis will be also performed with Cochrane Mantel–Haenszel for the univariate analysis and random-effects ordinal logistic regression adjusted on initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion) for **multiple regression**.

Time-to-event curves will be calculated with the use of the Kaplan-Meier method in univariable analysis. For **multiple regression**, marginal Cox proportional hazards mode, with centre as random-effect, will be performed with results reported as hazard ratios with 95%

confidence intervals, and proportional hazard assumption verified using the Schoenfeld test and plotting residuals.

Concerning the study of the parameters collected longitudinally, mixed models will be used to take into account between and within patient variability, in addition to centre random-effect. The following fixed effect will be analysed: randomisation group, time and their interaction.

Planned subgroup analyses will be done to explore potential influence of age, stroke laterality, stroke initial severity based on NIHSS, time delay, thrombus location and associated extracranial carotid artery stenosis/thrombosis on the incidence of the primary outcome. The study of interaction between randomization group and subgroup will be analysed.

If missing data are greater than 5%, an additional analysis will be performed using the multiple imputation method (Stata software, command mi).

A two-sided P value of less than 0.05 will be considered for statistical significance.

As proposed by some statisticians,[1,2] a particular focus will be given to the magnitude of differences, in addition to inferential statistical tests expressed using p-values.

Outcomes

Primary outcome measure: The primary outcome measure is a composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary outcome measures:

- Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure[3,4]:
    - Ordinal score on the mRS by day 90
    - Functional independence by day 90 defined as a mRS score 0-2
    - Excellent recovery by day 90 defined as a mRS score 0-1
    - Moderate recovery by day 90 defined as a mRS score 0-3
    - Shift analysis of day 90 mRS adjusted for initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion)
    - Good recovery defined with sliding dichotomy responder analysis relating day 90 mRS with baseline NIHSS score: mRS 0 for NIHSS ≤ 7; mRS 0-1 for NIHSS 8-14; mRS 0-2 for NIHSS > 14
- Intraprocedural hemodynamic and ventilatory conditions and complications defined as hypotension, blood pressure variability, hypoxemia and aspiration
- Intervention-associated vessel and others complications defined as arterial dissection or perforation, groin hematoma, embolization in another arterial territory
- Stroke onset to door delay, door to groin puncture delay, door to reperfusion delay, stroke onset to groin puncture delay, GA/CS induction to groin puncture delay, duration of the procedure, stroke onset to reperfusion delay
- Successful reperfusion defined by the modified Treatment In Cerebral Ischemia (mTICI) reperfusion scale of 2b or 3 (with a grade of 2b or 3 indicating reperfusion of > 50% of the affected territory)
- NIHSS by day 1 and day 7
- Stroke unit and hospital length of stay

- Perioperative complications by day 7 defined as pneumonia, acute cardiogenic pulmonary oedema, myocardial infarction, extra pulmonary infection, venous thromboembolism, new event of AIS, epilepsy, gastrointestinal bleeding or other symptomatic bleeding
- Malignant stroke evolution by day 7
- Symptomatic intracranial haemorrhage by day 7 defined as brain haemorrhage on imaging associated with an increase of at least 4 points in the NIHSS score
- Unexpected intensive care unit admission by day 7
- Mortality by day 7 and day 90
- Procedural feasibility score estimated by the radiologist and the anaesthesiologist and patient acceptability score

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5 and 19
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	19
Protocol version	#3	Date and version identifier	13
Funding	#4	Sources and types of financial, material, and other support	See note 1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 and 2

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	See note 2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See note 3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15 and 19
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7 and 8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7 and 8
Objectives	#7	Specific objectives or hypotheses	8 and 9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10 and 11

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11 and 18
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10 and 11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	See note 4
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14, 15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	See note 5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	See note 6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	See note 7
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18 and 19

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	26 and 27
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases,	20 and 21

		or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Author notes

1. 20, 26 and 27
2. 1, 2 and 20
3. 20, 25, 26, 27 and
4. 11, 12 and 13
5. 16, 17 and supplementary file
6. 17 and supplementary file
7. 18 and supplementary file

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Sedation versus general anaesthesia in endovascular therapy for anterior circulation acute ischemic stroke: the multicentre randomised controlled AMETIS trial study protocol

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Sedation versus general anaesthesia in endovascular therapy for anterior circulation acute ischemic stroke: the multicentre randomised controlled AMETIS trial study protocol

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ABSTRACT

Introduction: Endovascular thrombectomy is the standard of care for anterior circulation acute ischemic stroke (AIS) secondary to emergent large vessel occlusion in patients who qualify. General Anaesthesia (GA) or Conscious Sedation (CS) are usually required to ensure patient comfort and avoid agitation and movement during thrombectomy. However, the question of whether the use of GA or CS might influence functional outcome remains debated. Indeed, conflicting results exist between observational studies with better outcomes associated with CS and small monocentric randomized controlled trials favouring GA. Therefore, we aim to evaluate the effect of CS versus GA on functional outcome and peri-procedural complications in endovascular mechanical thrombectomy for anterior circulation AIS.

Methods and analysis: Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is an investigator initiated, multicentre, prospective, randomised controlled, two-arm trial. AMETIS trial will randomised 270 patients with anterior circulation AIS in a 1:1 ratio, stratified by centre, NIHSS (≤ 15 or > 15) and association of intravenous thrombolysis or not to receive either CS or GA. The primary outcome is a composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or cardiogenic acute pulmonary oedema or malignant stroke evolution occurring by day 7.

Ethics and dissemination: The AMETIS trial was approved by an independent ethics committee. Study began in august 2017. Results will be published in an international peer-reviewed medical journal.

Trial registration number: NCT03229148.

(Abstract word count: 265)

ARTICLE SUMMARY

Strengths and limitations of this study

- Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is the first multicentre randomised controlled trial comparing conscious sedation (CS) and general anaesthesia (GA) in thrombectomy for anterior circulation (internal carotid artery and/or proximal middle cerebral artery) acute ischemic stroke.
- The multicentre setting and large pragmatic inclusions criteria compatible with current practice and recommendations will allow external validity.
- Stratification based on centre, stroke severity and concomitant administration of intravenous thrombolysis will allow groups homogeneity and comparability.
- Composite primary outcome measure will allow evaluation of functional independence at 3 months and neurological and non-neurological peri-procedural complications. Secondary outcomes will measure different important aspects of care.
- Despite the absence of specific anaesthetic protocol concerning CS and GA management in order to reinforce external validity, perfusion pressure determinants (arterial blood pressure and carbon dioxide tension) will have to be maintained in strict limits.

INTRODUCTION

Background and rationale

Endovascular mechanical thrombectomy dramatically changed management of acute ischemic stroke (AIS). Randomised controlled trials demonstrated improved outcome associated with the procedure using stent-retrievers in anterior circulation AIS.[1-6] The American Heart Association/American Stroke Association, as others national medical societies, rapidly endorsed this strategy as a level 1 recommendation in association if possible with intravenous thrombolysis.[7] Nevertheless, peri-procedural management in the field added complexity since immobility and cardio-respiratory stability could be incompatible with acute neurological failure in these frail patients. Notably, the optimal management strategy during thrombectomy, using either General Anaesthesia (GA) or Conscious Sedation (CS), remains controversial. It was traditionally assumed that CS was superior since GA could negatively affect brain physiology especially cerebral blood flow (CBF) in the penumbra area related to induced systemic hypotension and carbon dioxide modulation.[8] Also, it was stressed the possible excessive delay associated with GA initiation that counteract a "time is brain" strategy. Nevertheless, evidence based medicine supporting this concept is scarce with methodological issues associated with observational data.[9] Notably, sickest patients were prone to receive GA and the anaesthetic strategy was not protocolized nor randomised.[10] We could conceptually argue possible benefits of GA providing systemic hypotension is treated and avoided: 1) immobility that could facilitate an easier, rapid and effective technical procedure, 2) airway protection since AIS patients are prone to aspiration pneumonia related to neurological injury, 3) patient comfort in a highly stressful environment with sometimes prolonged procedures.[9] Recently, 3 small monocentric randomised controlled trials specifically addressed effect of anaesthesia care on stroke outcome. First, the SIESTA trial randomised 150 patients between CS and GA.[11] No difference occurred in the National Institutes of Health Stroke Scale (NIHSS)

at 24 hours, which was the primary outcome. More patients were functionally independent after 3 months, defined as a Modified Rankin Scale (mRS, which ranges from 0 [no symptom] to 6 [death]) score 0 to 2, in the GA group. Second, the AnStroke trial randomised 90 patients between CS and GA.[12] No difference was achieved concerning the primary outcome mRS at 3 months and others secondary outcomes. Finally, the GOLIATH trial randomised 128 patients between CS and GA.[13] There was no difference in the volume of infarct growth as a primary outcome despite significantly higher successful reperfusion and better mRS score at 3 months in the GA group. On the assumption of these discrepancies, a multicentre randomised controlled trial comparing CS and GA is urgently needed.[14,15]

Objectives

Primary objective

The primary objective of the study is to determine whether CS or GA is associated with improved outcome defined as a composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or cardiogenic acute pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary objectives

The study will also explore if CS or GA in endovascular therapy for anterior circulation AIS is associated with difference in several outcomes: functional independence by day 90, intraprocedural hemodynamic and ventilatory conditions, intervention-associated vessel and others complications, procedural time delays, successful recanalization, stroke unit and hospital

length of stay, perioperative complications by day 7, unexpected intensive care unit admission by day 7, mortality by day 7 and day 90.

Trial design

The Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is an investigator initiated, national, multicentre, prospective, open-labelled, stratified, randomised controlled two-arm trial.

Consort diagram

Figure 1 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram of the AMETIS trial.[16]

METHODS AND ANALYSIS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

This manuscript was written in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.[17]

Study setting

The AMETIS trial takes place in 11 university hospitals in France (Clermont-Ferrand, Paris Pitié-Salpêtrière, Paris Saint-Antoine, Lyon, Toulouse, Marseille, Montpellier, Rouen, Lille, Poitiers and Saint-Etienne).

Eligibility criteria

Inclusion criteria

Adult patients admitted for anterior circulation (internal carotid artery and/or proximal middle cerebral artery) AIS, eligible for thrombectomy as decided by the neurology/neuroradiology teams based on current guidelines using brain imaging selection.[15]

Exclusion criteria

Patients with one or more criteria are not included:

- Age < 18 years.
- Coma or altered vigilance defined as a score ≥ 2 on the level of consciousness 1A subscale of the NIHSS.[18]
- Premorbid loss of autonomy defined as a mRS > 1.[19]
- Posterior circulation stroke.
- Associated cerebral haemorrhage.
- Stroke complicating another acute illness or postoperative stroke.
- Pregnant or breastfeeding women.
- Adult under the protection of the law.

Interventions

Patients eligible for inclusion will be randomly assigned to CS or GA after a routine medical anaesthetic emergency evaluation has been made by a certified senior Anaesthesiologist. As required by French law, all contraindications and/or known allergy to anaesthetics will be registered.

Modality of the CS and GA protocols are left to the attending anaesthesiologist in accordance with current and local guidelines providing systolic blood pressure is maintained between 140 and 180 mmHg (with vasopressor infusion if necessary) and arterial pulse oxymetry (SpO2) > 94 %.[15]

Under GA, tracheal intubation is mandated and mechanical ventilation should be managed to maintain an End Tidal CO2 (EtCO2) level between 30 and 35 mmHg.

Under CS, a minimal to moderate sedation level has to be targeted as defined by the American Society of Anesthesiologists (ASA) recommendations.[20] Clinical sedation level will be evaluated using the Richmond Agitation Sedation Scale (RASS) with an objective between 0 and -3 (defined as a patient alert and calm or drowsy with sustained awakening (eye opening/eye contact) to voice ≥ 10 seconds or briefly awake to voice with eye contact < 10 seconds or movement/eye opening to voice).[21,22] Effective spontaneous ventilation has to be maintained.

In the CS group, a crossover to GA with tracheal intubation is recommended in case of severe agitation, coma defined as a -4 or -5 RASS value (no response to voice but movement or eye opening to physical stimulation or no response to physical stimulation) despite stopping sedative drugs, loss of airway protective reflexes, respiratory failure and incoercible vomiting.

Stent retrievers are the preferred devices to perform thrombectomy. Nevertheless, alternative devices could be used.

At the end of intervention, GA and CS have to be immediately stopped and in the GA group extubation should occur as soon as possible.

After the intervention, depending on each hospital organization and anaesthesia modality (GA or CS), patients are transferred to the post anaesthesia care unit or neurological or general intensive care unit.

Outcomes

Primary outcome measure

The primary outcome measure is a binary composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary outcome measures

- mRS by day 90[19,23,24]
  - Ordinal score on the mRS by day 90
  - Functional independence by day 90 defined as a mRS score 0-2
  - Excellent recovery by day 90 defined as a mRS score 0-1
  - Moderate recovery by day 90 defined as a mRS score 0-3
  - Shift analysis of day 90 mRS adjusted for initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion)
  - Good recovery defined with sliding dichotomy responder analysis relating day 90 mRS with baseline NIHSS score: mRS 0 for NIHSS ≤ 7; mRS 0-1 for NIHSS 8-14; mRS 0-2 for NIHSS > 14
- Intraprocedural hemodynamic and ventilatory conditions and complications defined as hypotension, blood pressure variability, hypoxemia and aspiration
- Intervention-associated vessel and others complications defined as arterial dissection or perforation, groin hematoma, embolization in another arterial territory
- Stroke onset to door delay, door to groin puncture delay, door to reperfusion delay, stroke onset to groin puncture delay, GA/CS induction to groin puncture delay, duration of the procedure, stroke onset to reperfusion delay (see supplementary file 1 for definitions).

- Successful reperfusion defined by the modified Treatment In Cerebral Ischemia (mTICI) reperfusion scale of 2b or 3 (with a grade of 2b or 3 indicating reperfusion of > 50% of the affected territory)[25]
- NIHSS by day 1 and day 7[18]
- Stroke unit and hospital length of stay
- Perioperative complications by day 7 defined as pneumonia, acute cardiogenic pulmonary oedema, myocardial infarction, extra pulmonary infection, venous thromboembolism, new event of AIS, epilepsy, gastrointestinal bleeding or other symptomatic bleeding[26]
- Malignant stroke evolution by day 7[27]
- Symptomatic intracranial haemorrhage by day 7 defined as brain haemorrhage on imaging associated with an increase of at least 4 points in the NIHSS score[28]
- Unexpected intensive care unit admission by day 7
- Mortality by day 7 and day 90
- Procedural feasibility score estimated by the radiologist and the anaesthesiologist and patient acceptability score[29]

Recruitment

Patients are expected to be included during a 2-year period starting in august 2017.

2016-2017: Protocol, approvals from ethics committee (*CPP Sud-Est I*) and the French Medicine Agency (*Agence Nationale de Sécurité du Médicament et des produits de santé, ANSM*); trial tool development (online case report form and randomisation system).

2017-2019: Inclusion of patients.

2019: cleaning and closure of the database, data analyses, writing of the manuscript and submission for publication.

Trial status

The current protocol is version 4.0. Study started enrolment in august 2017. To date (28th October 2018), 186 patients have been randomised in the study.

Patient and public involvement

Patients will not be invited to comment on study design or conduction of the trial.

METHODS: ASSIGNEMENT OF INTERVENTIONS

Allocation and sequence generation

Randomisation will be conducted over a dedicated password-protected, SSL-encrypted website (CSOnline, Clinsight) to allow concealed allocation. Each patient will be given a unique patient number and randomisation number. The allocation sequence will be generated with the use of a minimisation algorithm stratified according to centre, NIHSS score (≤ 15 or > 15) and association of intravenous thrombolysis or not. The participant allocation will be carried out by local investigators who will log into the randomisation system using a personal ID and will enter any relevant information.

Blinding

This is an open label, unblinded trial for the patient and the physician in charge, related to the nature of the intervention (GA with endotracheal intubation or CS). Assessor blinded evaluation of the primary outcome will be performed since the assessor and statistician will be masked to the subjects' assignment group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

At each participating centre, data will be collected and entered into the web-based electronic case report form (eCRF) (CSOnline, Clinsight) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators. From the eCRF, the trial database will be created. Paper case report form will be used in case of technical problems with the eCRF. Trained research coordinators will monitor data collection. Data collected are presented in supplementary file 1.

Patient withdrawal:

Evaluated procedure is tested during endovascular thrombectomy. Nevertheless, participant can withdraw consent at any time without need for further explanation. Data will be destroyed and a new patient will be randomised for the complete sample size.

Statistical methods

Sample size estimation

According to literature analysis based on 5 international randomised controlled trials about endovascular thrombectomy in anterior circulation AIS, frequency of events constitutive of the composite primary outcome was expected at 50%.[1-5] Then, we postulated that 124 patients per group would provide 90% statistical power to detect an absolute between-group difference equals 20% (50% vs. 30%) for a two-sided type I error at 5%. Assuming lost to follow-up and modified intention to treat population requirements (as defined in supplementary file 2) between 5% and 10%, 270 patients have to be recruited for the study.

Interim analysis

A safety interim analysis is planned after 50% of inclusions. The independent Data and Safety Monitoring Board (DSMB) could recommend stopping the study if prolongation of the trial clearly compromises patient safety (in case of serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs)). The steering committee (SC) will be responsible to continue, hold or stop the study based on the DSMB recommendations.

Statistical analysis

A predefined statistical analysis plan will be followed (supplementary file 2). All analyses will be conducted with Stata software (version 13, StataCorp, College Station, USA) and R (http://cran.r-project.org/) before the breaking of randomisation code, in line with the International Conference on Harmonization Good Clinical Practice guidelines. A two-sided p value of less than 0.05 will be considered for statistical significance.

Primary analysis will be done in modified intention to treat (mITT). Then, a per-protocol analysis will also be done to take into account protocol deviations notably crossover from CS to GA. Patients who withdraw consent will not be included in these analyses.

Continuous variables will be presented as mean and standard-deviation or as median and quartiles otherwise. Normality will be assessed using the Shapiro-Wilk test and homoscedasticity will be assessed using the Fisher-Snedecor test.

Concerning the comparison of the primary composite outcome between CS and GA, a Chi2 test or a Fischer's exact test will be performed as appropriate. Adjusted analysis will be conducted with the use of robust (standard errors) random-effects Poisson generalised linear regression (package gllamm) will be used (1) to take into account adjustment on possible confounding covariates selected according to clinical relevance and stratification variables (including stratification parameters) and (2) to consider within and between centre variability (as random-effect). A particular attention will be paid to the covariates used in multivariable regressions,

especially quantitative covariates for which convergence issues can be raised. As presented in statistical analysis plan, normally, only "time delays" will be concerned. Sensitivity analysis considering these covariates, dichotomizing according to the statistical distribution and to the clinical relevance, should be proposed. The results will be presented as relative risks and 95% confidence interval (CIs). The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome.

Concerning the comparisons of secondary outcomes between groups, Student t test or non-parametric Mann-Whitney test as appropriate will be used for quantitative parameters such as intraoperative blood pressure, oxygen saturation, timing delays or length of stays. Chi-squared test or Fischer's exact test will be used for categorical parameters such as NIHSS and ordinal and nominal (dichotomized) mRS, intervention-associated and perioperative complications, mTICI score, functional independence at day 90 and mortality. Results will be reported as effect-sizes and absolute differences with 95% CIs. Then, multiple regression will be conducted using random-effects models taking into account between and within centre variability: linear mixed models for quantitative endpoints and generalized linear mixed regression for categorical endpoints. The results will be expressed, respectively, as regression coefficients and relative risks, with 95% CIs.

Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure, this parameter will be treated by different ways according to literature notably as an ordinal variable.[15,30] A shift analysis will also be performed: Cochrane Mantel–Haenszel for the univariate analysis and random-effects ordinal logistic regression adjusted on initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion) for multiple regression.

Time-to-event curves will be calculated with the use of the Kaplan-Meier method in univariable analysis. For multiple regression, marginal Cox proportional hazards model (with centre as random effect) will be performed. Proportional hazard assumption will be verified using the

Schoenfeld test and plotting residuals. Results will be reported as HRs with 95% CIs.

Concerning the study of parameters collected longitudinally (in particular NIHSS score at day 1 and day 7, arterial pressure and arterial oxygen saturation), mixed models will be used to take into account between and within patient variability, in addition to centre random-effect. The following fixed effect will be analysed: randomisation group, time and their interaction (time x group).

According to clinical relevance and to European Medicines Agency (EMA) and Consolidated Standards of Reporting Trials (CONSORT) recommendations, post-hoc analyses will be proposed after the study of subgroup × randomisation group interaction in regression models (for repeated data or not).

Missing values will be notified and analysed. A sensitivity analysis will be performed and the nature of missing data will be studied (missing at random or not). If the frequency is > 5%, additional analyses will be performed using the multiple imputation method. [31]

METHODS: MONITORING

Data monitoring

Before the start of the study, anaesthetic, neurological and radiological medical and paramedical teams are trained at each site for the study protocol by study coordinators. Physicians are in charge of patient screening and inclusion. Patients admitted for stroke treated by endovascular mechanical thrombectomy and not included in the study will be recorded anonymously at each centre into a screening log. Data will be collected in a web-based eCRF by trial personnel. Each centre will only have access to site-specific data. Each patient will receive a unique trial identification number. Only the investigators and research team will have access to any protected health information of study participants and any study data.

Data monitoring and quality control will be conducted in each centre after the first 10 inclusions then after the next 20 inclusions and at the end of the study by official representatives of the study promoter (Department of Clinical Research and Innovation, Clermont-Ferrand University Hospital).

Data will be handled according to the French law. All originals records (including consent forms, reports of SUSARs and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years. Only the principal investigators and the statistician will have access to the final dataset.

Harms

Every adverse events that could be related to the trial will be reported to the trial coordinating centre. According to the French law, all suspected serious adverse events will be reported to the ANSM. The DSMB will also be informed. DSMB is independent from the trial investigators and will perform an ongoing review of safety parameters and study conduct. DSMB members are 2 independent physicians in Anaesthesia / Critical Care Medicine and Neurology, and a Biostatician that have skills and expertise in Anaesthesia, clinical Neuroscience and clinical research. The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety of the interventions during the trial and for monitoring the overall conduct of the trial. DSMB could also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. No formal criteria are set to stop the study. However, recommendations for pausing or stopping the study could be made by DSMB in case of SARs and SUSAR. The scientific committee will be responsible for promptly reviewing the DSMB recommendations and to decide whether to continue, hold or stop the study, and to determine whether amendments to the protocol are needed.

ETHICS AND DISSEMINATION

Research ethics approval

The AMETIS study is conducted in accordance with the Declaration of Helsinki and was registered at http://www.clinicaltrial.gov on 25 July 2017 and last updated on 5 September 2017 with trial identification number NCT03229148. The trial was approved by the ethics committee *CPP Sud-Est I* on 22 May 2017 (approval number 2017-11) and ANSM on 6 march 2017 (approval number 2016-A02064-47). Any change to eligibility criteria, outcomes and analyses will be communicated to investigators, the ethics committee and the ANSM to obtain their approval.

Consent or assent

Whenever possible to include the patient, written inform consent will be searched. Nevertheless, related to neurological injury and emergency, the patient may be unable to provide written informed consent. In this case, written informed consent could be obtained from the patient next of kin if immediately available. Otherwise, an emergency consent procedure is used with investigator signature countersigned by an independent physician. As soon as possible after recovery, written informed consent from the patient will be searched to continue the study. This consent strategy was approved by the Institutional Review Board and the ethics committee *CPP Sud-Est I* on 22 May 2017 in accordance with the 2013 Declaration of Helsinki.

Funding

The study is an investigator-initiated trial with study promotion performed by Clermont-Ferrand university hospital, Clermont-Ferrand, France. There is no industry support or involvement in the trial. This study is supported by grants from the French Ministry of Health

(Projet Hospitalier de Recherche Clinique Interrégional 2016). The funders have no influence on study protocol, conduct and results analysis.

Dissemination policy

On study completion, manuscript will be submitted to one peer-reviewed journal regardless of the results. All trial sites will be acknowledged and every investigators name will appear under "AMETIS trial group" in the final manuscript. AMETIS study scientific committee will grant authorship depending on personal input according to the Vancouver guidelines. If a trial site investigator is to gain authorship, the site has to include 30 patients or more. If the site includes 50 patients or more, two authorships will be granted. A writing committee will be composed of members of the scientific committee and investigators to define the order of authors of any publications. Trial results will also be presented at local, national and international meetings.

DISCUSSION

We recently observed the "thrombectomy revolution" in anterior circulation AIS.[32] Emergency interventional procedures in frail stroke patients often require skills from Anaesthesia providers since immobility is needed and severe intra-procedural complications may occur (for example coma, agitation or aspiration pneumonia).

Taking into account the increasing volume of procedures and the potential effect of the anaesthetic strategy on outcome with discrepancy in literature, it appears essential to provide a multicentre randomised controlled trial to enhance external validity as suggested by recent recommandations.[15]

Concurrent ongoing trials with day 90 mRS as a primary outcome are planning to recruit 635 patients to demonstrate non-inferiority between CS and GA,[33] 350 patients to demonstrate

superiority of CS vs GS (NCT02822144) or 260 patients to demonstrate superiority of GA vs CS (NCT03263117).

Some limitations could be opposed to the AMETIS trial protocol. First, no specific anaesthetic protocol will be used. We choose this strategy in a pragmatic way since no data demonstrate that a drug is better than another even if modulation of CBF could be variable. However, the protocol requires strict objectives for systolic blood pressure and "normal" blood carbon dioxide tension in GA group.[34,35] Drugs and dose will be monitored. Second, no maximal time delay from stroke onset or maximal/minimal NIHSS values are recommended in order to adhere to a pragmatic investigator-based approach. This strategy complies with recent trials and recommendations: patient selection for thrombectomy is made on angioCT or MRI scans with eventual mismatch evaluation especially when delay is > 6 hours and for wake-up strokes.[15,36,37] Delays and imaging modality used for selection will be monitored. Notably, despite published trials mentioned NIHSS limits as inclusion/exclusion criteria, providing thrombectomy is indicated based on actual recommendations, the optimal anaesthetic strategy deserves evaluation whatever the NIHSS is. Stratification on NIHSS score with a cut-off of 15 will provide homogeneous groups in term of initial severity. As recommended, outcome measures will include adjustments for baseline severity.[15] Third, despite thrombectomy might benefit to patients with premorbid mRS>1, we excluded these patients since evaluation is difficult in emergency condition and inclusion of dependent patients could strongly affect the primary outcome. This strategy was adopted by others.[3-5,37] Fourth, we choose a composite principal outcome measure since anaesthesia strategy could affect functional independence at 3 months but also peri-interventional morbidity. The effect size that we could expect on functional independence at 3 months is probably far less than thrombectomy on its own. Based on actual literature, SIESTA trial found dramatically decreased functional independence associated with CS with only 18% of mRS 0-2 compared to 37% in GA.[11] 18% of patients being independent

is far less than in thrombectomy trials where it barely represents controlled groups (intravenous thrombolysis alone).[1-6] With these proportions, 240 patients would have been necessary to demonstrate a statistical difference with a beta power of 90% but we could expect important centre effect in SIESTA trial. On the contrary, ANSTROKE trial didn't find any difference between groups, with functional independence in respectively 42 and 40% of patients between GA and CS.[12] Based on these 2 trials, functional independence could be obtained in roughly 40% of patients under GA. Providing a 20% variation in positive or negative effect on functional independence, more than 1000 patients would be required with a 80% beta power. An anaesthesia size effect of more than 20% appeared unrealistic.

Fifth, even if possible in selected patients, we will not study local anaesthesia alone. Management solely under local anaesthesia is difficult regarding comfort and immobility particularly in sickest patients, in left hemisphere strokes with aphasia and in tandem lesions (associated cervical carotid artery occlusion). In the CS group, we provide only clinical sedation objectives based on RASS score between 0 and -3. There is no recommended drug to achieve this goal and local anaesthesia is systematically used under CS.

In conclusion, AMETIS trial is the first multicentre randomised controlled study exploring the effect of CS versus GA on functional outcome and peri-procedural complications in endovascular mechanical thrombectomy for anterior circulation AIS. The results of this study could have significant clinical and public health implications.

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AUTHOR CONTRIBUTIONS

RC, EF, SJ, LV, AF and VD are members of AMETIS trial scientific committee and contributed to the conception and design of the research protocol. RC, CFC and EF provided critical skills concerning trial interventions and procedures. CFC and RC wrote the first version of the protocol. RC wrote this manuscript. BP designed the statistical analysis plan. SM, ACL, PFP, SM, BT, CDF, FV, EC, AM, MB, EC and JEB are involved in acquisition, analysis and interpretation of the data. All authors revised the final protocol and approved his submission.

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AMETIS trial collaborators are listed under ANARLF Network and AMETIS study group:

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COMPETING INTERESTS

RC reports personal fees from MSD and Smiths Medical France for education events, transport and accommodation fees from Novartis, Depuy France and Vasopharm outside the submitted work.

KEYWORDS

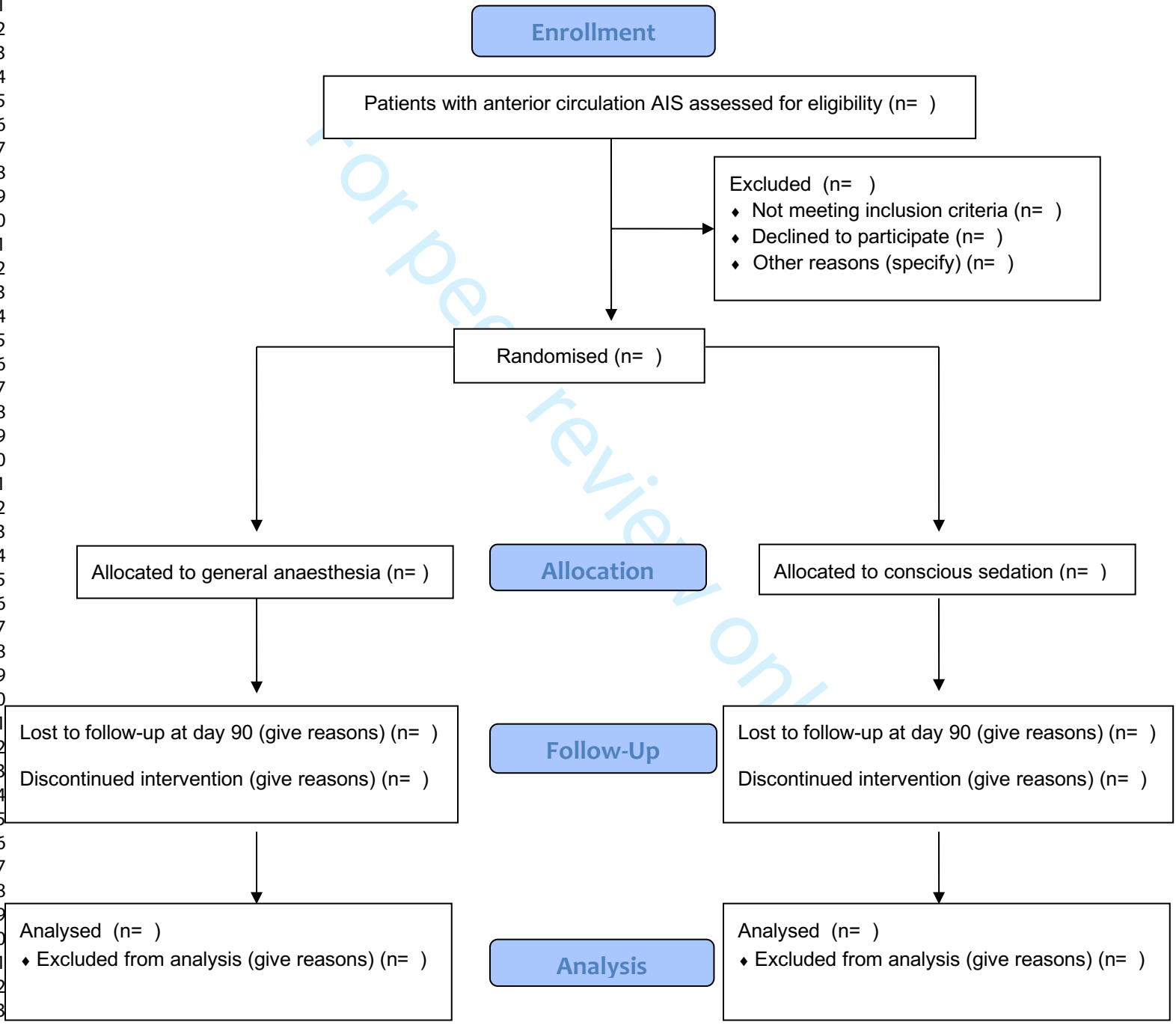
Stroke – Sedation – General Anaesthesia - Thrombectomy

WORD COUNT

3990

FIGURE LEGENDS

Figure 1: CONSORT diagram of the Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial illustrating the randomisation and flow of patients in the study. AIS: Acute Ischemic Stroke



Supplementary file 1: AMETIS trial data collection

At randomisation: Date and time of actual hospital admission, Transfer from another hospital: Y/N, Demographic data (age, height, gender and body mass index), comorbidities (hypertension: Y/N, renal failure: Y/N, cardiac failure: Y/N, diabetes mellitus: Y/N, alcohol abuse: Y/N, active smoking: Y/N, chronic obstructive pulmonary disease: Y/N), ongoing respiratory infection: Y/N, anticoagulation therapy: Y/N, antiplatelet therapy: Y/N, NIHSS score (stratification variable), premorbid mRS, brain imaging used for patient selection with corresponding ASPECT score (MRI: Y/N, AngioCT: Y/N, PerfusionCT: Y/N)[1,2], associated cervical vascular imaging: Y/N, localisation of AIS, intravenous thrombolysis (stratification variable) : Y/N, wake-up stroke: Y/N.

Intraoperative anaesthetic data: date and time of CS/GA, type (Propofol: Y/N, Thiopental: Y/N, Etomidate: Y/N, Midazolam: Y/N, Ketamine: Y/N, inhaled anaesthetics: Y/N, Sufentanil: Y/N, Remifentanil: Y/N, Succinylcholine: Y/N, Atracurium: Y/N, Cisatracurium: Y/N, Rocuronium: Y/N or others) and dose of anaesthetic drugs used, systolic, diastolic and mean arterial blood pressure every 5 minutes until 30 minutes and then every 10 minutes until the end of procedure, hypotension:Y/N (defined as one episode of systolic blood pressure < 120 mmHg during the prespecified time points of blood pressure measurement),[3] maximal blood pressure difference defined as maximal preintervention systolic blood pressure minus minimal perprocedural systolic blood pressure, intraprocedural maximal systolic and diastolic blood pressure, intraprocedural minimal systolic and diastolic blood pressure, pulse oxymetry every 5 minutes for 30 minutes and then every 10 minutes until the end of procedure, RASS score before arterial puncture and at the end of procedure before CS/GA removal, duration of CS or GA, volume of fluids used, type (Norepinephrine: Y/N, Ephedrine: Y/N, Phenylephrine: Y/N or others) and dose of vasoconstrictor if any, type (Nicardipine: Y/N, Urapidil: Y/N or others) and dose of antihypertensive drugs if any, intraprocedural complications (nausea: Y/N,

vomiting: Y/N, aspiration: Y/N, anaphylaxis: Y/N or others), tracheal intubation complication: Y/N, CS conversion to GA: Y/N, feasibility score estimated by the anaesthesiologist at the end of procedure.

Intraoperative neurological and radiological data: date and time of groin puncture and reperfusion if any, date and time of end of procedure (defined as the last set of radiological images), devices used for procedure (stent retrievers: Y/N, contact aspiration: Y/N, intra-arterial thrombolysis: Y/N, stenting: Y/N or others), number of desobstruction attempts, intervention-associated vessel complications (arterial dissection: Y/N, arterial perforation: Y/N, groin hematoma: Y/N, embolization in another arterial territory: Y/N), mTICI score at the end of procedure (ranging from 0 (no perfusion) to 3 (full perfusion with filling of all distal branches)), agitation during procedure (define as a RASS score > +1 at any moment (restless to combative patient) : Y/N), procedure difficulty associated with patient movement: Y/N, complexity of arterial catheterisation: Y/N, altered quality of images: Y/N, feasibility score estimated by the radiologist at the end of procedure.

Procedural time delays: Stroke onset to door delay is time from stroke symptom (or last time seen well for wake-up strokes) to actual hospital admission, Door to groin puncture delay is time from actual hospital admission to groin puncture, Stroke onset to groin puncture delay is time from stroke symptom (or last time seen well for wake-up strokes) to groin puncture, Door to reperfusion delay is time from actual hospital admission to reperfusion, GA/CS induction to groin puncture delay is time from administration of the first anaesthetic/sedative agent to groin puncture, Duration of the procedure is time from groin puncture to end of procedure (defined as the last set of radiological images), Stroke onset to reperfusion delay is time from stroke symptom (or last time seen well for wake-up strokes) to reperfusion (if any).

Postoperative data at day 1 and by day 7 or hospital discharge if prior: NIHSS, groin hematoma: Y/N, pneumonia treated with antibiotics: Y/N, myocardial infarction: Y/N, acute

cardiogenic pulmonary oedema (defined as evidence of fluid accumulation in the alveoli due to poor cardiac function)[4]: Y/N, extra pulmonary infection: Y/N, venous thromboembolism: Y/N, new event of AIS: Y/N, epilepsy: Y/N, gastrointestinal bleeding or other symptomatic bleeding: Y/N, malignant stroke evolution: Y/N, symptomatic intracranial haemorrhage: Y/N, stroke unit and hospital length of stay, unexpected intensive care unit admission: Y/N, care limitation/palliation: Y/N, mortality: Y/N, patient acceptability score.

Postoperative data at day 90: mRS score, hospital length of stay, mortality: Y/N.

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Supplementary file 2: AMETIS trial statistical analysis plan

Populations

Primary analysis will be done in modified intention to treat (ITT). Then, a per-protocol analysis will also be done to take into account protocol deviations notably crossover from CS to GA. Patients who withdraw consent will not be included in the analysis.

Intention-to treat (ITT) population: All randomised patients. This population will not be analysed in the AMETIS study.

Modified intention-to-treat population: All randomised patients except patients who:

- Withdrew consent for the use of data

  OR

- Would never have any of the intervention (CS nor GA, for example due to spontaneous or thrombolytic associated reperfusion after randomisation but before the anaesthetic procedure)

  OR

- Would have the intervention (CS or GA) without any attempt of mechanical thrombectomy due to spontaneous or thrombolytic associated reperfusion.

Per-protocol population: All randomised patients except patients having one or more major protocol violations defined as:

- Patients who would not be eligible for randomization according to inclusion/non-inclusion criteria

  OR

- Patients who accidentally would have received the wrong intervention (CS or GA)

  OR

- Would never have any of the intervention (CS nor GA, for example due to spontaneous or thrombolytic associated reperfusion after randomisation but before the anaesthetic procedure)

  OR

- Would have the intervention (CS or GA) without any attempt of mechanical thrombectomy due to spontaneous or thrombolytic associated reperfusion

  OR

- Patients who would be withdrawn from the protocol because the patient would have withdrawn consent.

Statistical analyses

Primary analysis

Unadjusted Chi-square test (or Fisher's exact test as appropriate) for binary outcome. For rate data, the generalized linear (Stata software: command glm) model will be used with Poisson distribution (link=log and offset), including a random effect to account for centre effect. Results will be expressed as Relative Risks and 95% confidence intervals.

Secondary analyses

- For the primary outcome

Multiple logistic mixed regression will be used with the following covariates (criterion for entering variables tested in the model will be selected if $P<0.10$ and according to clinically relevant covariates with anticipated relationship with outcome), including stratification

parameters, centre treated as a random effect. Particular attention will be paid to the study of multicollinearity.

Binary covariates

- Gender M/F
- Comorbidities Y/N
- Anticoagulation therapy Y/N
- Antiplatelet therapy Y/N
- Intravenous thrombolysis Y/N (stratification variable)
- Wake up stroke Y/N
- Quality of reperfusion: mTICI (good or bad)
- Left sided stroke Y/N
- Carotid top occlusion Y/N

Continuous covariates (with logarithmic transformation when appropriate)

- Demographic data
- Time delays

Ordinal covariates

- NIHSS score (stratification variable)
- Baseline mRS
- ASPECT score
- Localisation of AIS
- mTICI score

- For secondary outcomes

A chi-squared test (or Fisher's exact test, as appropriate) will be used for secondary binary outcomes. The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome (mRS score 0 to 2 by day 90, perioperative complications: intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7). Adjusted analyses will be performed with the use of random-effect Poisson generalized linear model regression and will be presented as Relative Risks and 95% confidence intervals, using the same adjustment variables.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired t test or the Mann-Whitney U test as appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Adjusted analyses, using multiple linear regression, will be conducted using the same adjustment variables and center as random-effect. Results will be expressed as regression coefficients and 95% confidence intervals.

Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure, this parameter will be treated by different ways according to literature notably as an ordinal variable. A shift analysis will be also performed with Cochrane Mantel–Haenszel for the univariate analysis and random-effects ordinal logistic regression adjusted on initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion) for **multiple regression**.

Time-to-event curves will be calculated with the use of the Kaplan-Meier method in univariable analysis. For **multiple regression**, marginal Cox proportional hazards mode, with centre as random-effect, will be performed with results reported as hazard ratios with 95%

confidence intervals, and proportional hazard assumption verified using the Schoenfeld test and plotting residuals.

Concerning the study of the parameters collected longitudinally, mixed models will be used to take into account between and within patient variability, in addition to centre random-effect. The following fixed effect will be analysed: randomisation group, time and their interaction.

Planned subgroup analyses will be done to explore potential influence of age, stroke laterality, stroke initial severity based on NIHSS, time delay, thrombus location and associated extracranial carotid artery stenosis/thrombosis on the incidence of the primary outcome. The study of interaction between randomization group and subgroup will be analysed.

If missing data are greater than 5%, an additional analysis will be performed using the multiple imputation method (Stata software, command mi).

A two-sided P value of less than 0.05 will be considered for statistical significance.

As proposed by some statisticians,[1,2] a particular focus will be given to the magnitude of differences, in addition to inferential statistical tests expressed using p-values.

Outcomes

Primary outcome measure: The primary outcome measure is a composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary outcome measures:

- Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure[3,4]:
  - Ordinal score on the mRS by day 90
  - Functional independence by day 90 defined as a mRS score 0-2
  - Excellent recovery by day 90 defined as a mRS score 0-1
  - Moderate recovery by day 90 defined as a mRS score 0-3
  - Shift analysis of day 90 mRS adjusted for initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion)
  - Good recovery defined with sliding dichotomy responder analysis relating day 90 mRS with baseline NIHSS score: mRS 0 for NIHSS ≤ 7; mRS 0-1 for NIHSS 8-14; mRS 0-2 for NIHSS > 14
- Intraprocedural hemodynamic and ventilatory conditions and complications defined as hypotension, blood pressure variability, hypoxemia and aspiration
- Intervention-associated vessel and others complications defined as arterial dissection or perforation, groin hematoma, embolization in another arterial territory
- Stroke onset to door delay, door to groin puncture delay, door to reperfusion delay, stroke onset to groin puncture delay, GA/CS induction to groin puncture delay, duration of the procedure, stroke onset to reperfusion delay
- Successful reperfusion defined by the modified Treatment In Cerebral Ischemia (mTICI) reperfusion scale of 2b or 3 (with a grade of 2b or 3 indicating reperfusion of > 50% of the affected territory)
- NIHSS by day 1 and day 7
- Stroke unit and hospital length of stay

- Perioperative complications by day 7 defined as pneumonia, acute cardiogenic pulmonary oedema, myocardial infarction, extra pulmonary infection, venous thromboembolism, new event of AIS, epilepsy, gastrointestinal bleeding or other symptomatic bleeding
- Malignant stroke evolution by day 7
- Symptomatic intracranial haemorrhage by day 7 defined as brain haemorrhage on imaging associated with an increase of at least 4 points in the NIHSS score
- Unexpected intensive care unit admission by day 7
- Mortality by day 7 and day 90
- Procedural feasibility score estimated by the radiologist and the anaesthesiologist and patient acceptability score

1. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990; 1(1): 43-6.
2. Feise RJ. Do multiple outcome measures require p-value adjustment? *BMC medical research methodology* 2002; 2: 8.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018.
4. Nunn A, Bath PM, Gray LJ. Analysis of the Modified Rankin Scale in Randomised Controlled Trials of Acute Ischaemic Stroke: A Systematic Review. *Stroke research and treatment* 2016; 2016: 9482876.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5 and 19
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	19
Protocol version	#3	Date and version identifier	13
Funding	#4	Sources and types of financial, material, and other support	See note 1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 and 2

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	See note 2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See note 3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15 and 19
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7 and 8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7 and 8
Objectives	#7	Specific objectives or hypotheses	8 and 9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10 and 11

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11 and 18
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10 and 11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	See note 4
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14, 15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	See note 5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	See note 6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	See note 7
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18 and 19

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	26 and 27
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases,	20 and 21

		or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Author notes

1. 20, 26 and 27
2. 1, 2 and 20
3. 20, 25, 26, 27 and
4. 11, 12 and 13
5. 16, 17 and supplementary file
6. 17 and supplementary file
7. 18 and supplementary file

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Sedation versus general anaesthesia in endovascular therapy for anterior circulation acute ischemic stroke: the multicentre randomised controlled AMETIS trial study protocol

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Sedation versus general anaesthesia in endovascular therapy for anterior circulation acute ischemic stroke: the multicentre randomised controlled AMETIS trial study protocol

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ABSTRACT

Introduction: Endovascular thrombectomy is the standard of care for anterior circulation acute ischemic stroke (AIS) secondary to emergent large vessel occlusion in patients who qualify. General Anaesthesia (GA) or Conscious Sedation (CS) are usually required to ensure patient comfort and avoid agitation and movement during thrombectomy. However, the question of whether the use of GA or CS might influence functional outcome remains debated. Indeed, conflicting results exist between observational studies with better outcomes associated with CS and small monocentric randomized controlled trials favouring GA. Therefore, we aim to evaluate the effect of CS versus GA on functional outcome and peri-procedural complications in endovascular mechanical thrombectomy for anterior circulation AIS.

Methods and analysis: Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is an investigator initiated, multicentre, prospective, randomised controlled, two-arm trial. AMETIS trial will randomised 270 patients with anterior circulation AIS in a 1:1 ratio, stratified by centre, NIHSS (≤ 15 or > 15) and association of intravenous thrombolysis or not to receive either CS or GA. The primary outcome is a composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or cardiogenic acute pulmonary oedema or malignant stroke evolution occurring by day 7.

Ethics and dissemination: The AMETIS trial was approved by an independent ethics committee. Study began in august 2017. Results will be published in an international peer-reviewed medical journal.

Trial registration number: NCT03229148.

(Abstract word count: 265)

ARTICLE SUMMARY

Strengths and limitations of this study

- Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is the first multicentre randomised controlled trial comparing conscious sedation (CS) and general anaesthesia (GA) in thrombectomy for anterior circulation (internal carotid artery and/or proximal middle cerebral artery) acute ischemic stroke.
- The multicentre setting and large pragmatic inclusions criteria compatible with current practice and recommendations will allow external validity.
- Stratification based on centre, stroke severity and concomitant administration of intravenous thrombolysis will allow groups homogeneity and comparability.
- Composite primary outcome measure will allow evaluation of functional independence at 3 months and neurological and non-neurological peri-procedural complications. Secondary outcomes will measure different important aspects of care.
- Despite the absence of specific anaesthetic protocol concerning CS and GA management in order to reinforce external validity, perfusion pressure determinants (arterial blood pressure and carbon dioxide tension) will have to be maintained in strict limits.

INTRODUCTION

Background and rationale

Endovascular mechanical thrombectomy dramatically changed management of acute ischemic stroke (AIS). Randomised controlled trials demonstrated improved outcome associated with the procedure using stent-retrievers in anterior circulation AIS.[1-6] The American Heart Association/American Stroke Association, as others national medical societies, rapidly endorsed this strategy as a level 1 recommendation in association if possible with intravenous thrombolysis.[7] Nevertheless, peri-procedural management in the field added complexity since immobility and cardio-respiratory stability could be incompatible with acute neurological failure in these frail patients. Notably, the optimal management strategy during thrombectomy, using either General Anaesthesia (GA) or Conscious Sedation (CS), remains controversial. It was traditionally assumed that CS was superior since GA could negatively affect brain physiology especially cerebral blood flow (CBF) in the penumbra area related to induced systemic hypotension and carbon dioxide modulation.[8] Also, it was stressed the possible excessive delay associated with GA initiation that counteract a "time is brain" strategy. Nevertheless, evidence based medicine supporting this concept is scarce with methodological issues associated with observational data.[9] Notably, sickest patients were prone to receive GA and the anaesthetic strategy was not protocolized nor randomised.[10] We could conceptually argue possible benefits of GA providing systemic hypotension is treated and avoided: 1) immobility that could facilitate an easier, rapid and effective technical procedure, 2) airway protection since AIS patients are prone to aspiration pneumonia related to neurological injury, 3) patient comfort in a highly stressful environment with sometimes prolonged procedures.[9] Recently, 3 small monocentric randomised controlled trials specifically addressed effect of anaesthesia care on stroke outcome. First, the SIESTA trial randomised 150 patients between CS and GA.[11] No difference occurred in the National Institutes of Health Stroke Scale (NIHSS)

at 24 hours, which was the primary outcome. More patients were functionally independent after 3 months, defined as a Modified Rankin Scale (mRS, which ranges from 0 [no symptom] to 6 [death]) score 0 to 2, in the GA group. Second, the AnStroke trial randomised 90 patients between CS and GA.[12] No difference was achieved concerning the primary outcome mRS at 3 months and others secondary outcomes. Finally, the GOLIATH trial randomised 128 patients between CS and GA.[13] There was no difference in the volume of infarct growth as a primary outcome despite significantly higher successful reperfusion and better mRS score at 3 months in the GA group. On the assumption of these discrepancies, a multicentre randomised controlled trial comparing CS and GA is urgently needed.[14,15]

Objectives

Primary objective

The primary objective of the study is to determine whether CS or GA is associated with improved outcome defined as a dichotomous composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or cardiogenic acute pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary objectives

The study will also explore if CS or GA in endovascular therapy for anterior circulation AIS is associated with difference in several outcomes: functional independence by day 90, intraprocedural hemodynamic and ventilatory conditions, intervention-associated vessel and others complications, procedural time delays, successful recanalization, stroke unit and hospital

length of stay, perioperative complications by day 7, unexpected intensive care unit admission by day 7, mortality by day 7 and day 90.

Trial design

The Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial is an investigator initiated, national, multicentre, prospective, open-labelled, stratified, randomised controlled two-arm trial.

Consort diagram

Figure 1 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram of the AMETIS trial.[16]

METHODS AND ANALYSIS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

This manuscript was written in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.[17]

Study setting

The AMETIS trial takes place in 11 university hospitals in France (Clermont-Ferrand, Paris Pitié-Salpêtrière, Paris Saint-Antoine, Lyon, Toulouse, Marseille, Montpellier, Rouen, Lille, Poitiers and Saint-Etienne).

Eligibility criteria

Inclusion criteria

Adult patients admitted for anterior circulation (internal carotid artery and/or proximal middle cerebral artery) AIS, eligible for thrombectomy as decided by the neurology/neuroradiology teams based on current guidelines using brain imaging selection.[15]

Exclusion criteria

Patients with one or more criteria are not included:

- Age < 18 years.
- Coma or altered vigilance defined as a score ≥ 2 on the level of consciousness 1A subscale of the NIHSS.[18]
- Premorbid loss of autonomy defined as a mRS > 1.[19]
- Posterior circulation stroke.
- Associated cerebral haemorrhage.
- Stroke complicating another acute illness or postoperative stroke.
- Pregnant or breastfeeding women.
- Adult under the protection of the law.

Interventions

Patients eligible for inclusion will be randomly assigned to CS or GA after a routine medical anaesthetic emergency evaluation has been made by a certified senior Anaesthesiologist. As required by French law, all contraindications and/or known allergy to anaesthetics will be registered.

Modality of the CS and GA protocols are left to the attending anaesthesiologist in accordance with current and local guidelines providing systolic blood pressure is maintained between 140 and 180 mmHg (with vasopressor infusion if necessary) and arterial pulse oxymetry (SpO2) > 94 %.[15]

Under GA, tracheal intubation is mandated and mechanical ventilation should be managed to maintain an End Tidal CO2 (EtCO2) level between 30 and 35 mmHg.

Under CS, a minimal to moderate sedation level has to be targeted as defined by the American Society of Anesthesiologists (ASA) recommendations.[20] Clinical sedation level will be evaluated using the Richmond Agitation Sedation Scale (RASS) with an objective between 0 and -3 (defined as a patient alert and calm or drowsy with sustained awakening (eye opening/eye contact) to voice ≥ 10 seconds or briefly awake to voice with eye contact < 10 seconds or movement/eye opening to voice).[21,22] Effective spontaneous ventilation has to be maintained.

In the CS group, a crossover to GA with tracheal intubation is recommended in case of severe agitation, coma defined as a -4 or -5 RASS value (no response to voice but movement or eye opening to physical stimulation or no response to physical stimulation) despite stopping sedative drugs, loss of airway protective reflexes, respiratory failure and incoercible vomiting.

Stent retrievers are the preferred devices to perform thrombectomy. Nevertheless, alternative devices could be used.

At the end of intervention, GA and CS have to be immediately stopped and in the GA group extubation should occur as soon as possible.

After the intervention, depending on each hospital organization and anaesthesia modality (GA or CS), patients are transferred to the post anaesthesia care unit or neurological or general intensive care unit.

Outcomes

Primary outcome measure

The primary outcome measure is a binary composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary outcome measures

- mRS by day 90[19,23,24]
  - Ordinal score on the mRS by day 90
  - Functional independence by day 90 defined as a mRS score 0-2
  - Excellent recovery by day 90 defined as a mRS score 0-1
  - Moderate recovery by day 90 defined as a mRS score 0-3
  - Shift analysis of day 90 mRS adjusted for initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion)
  - Good recovery defined with sliding dichotomy responder analysis relating day 90 mRS with baseline NIHSS score: mRS 0 for NIHSS ≤ 7; mRS 0-1 for NIHSS 8-14; mRS 0-2 for NIHSS > 14
- Intraprocedural hemodynamic and ventilatory conditions and complications defined as hypotension, blood pressure variability, hypoxemia and aspiration
- Intervention-associated vessel and others complications defined as arterial dissection or perforation, groin hematoma, embolization in another arterial territory
- Stroke onset to door delay, door to groin puncture delay, door to reperfusion delay, stroke onset to groin puncture delay, GA/CS induction to groin puncture delay, duration of the procedure, stroke onset to reperfusion delay (see supplementary file 1 for definitions).

- Successful reperfusion defined by the modified Treatment In Cerebral Ischemia (mTICI) reperfusion scale of 2b or 3 (with a grade of 2b or 3 indicating reperfusion of > 50% of the affected territory)[25]
- NIHSS by day 1 and day 7[18]
- Stroke unit and hospital length of stay
- Perioperative complications by day 7 defined as pneumonia, acute cardiogenic pulmonary oedema, myocardial infarction, extra pulmonary infection, venous thromboembolism, new event of AIS, epilepsy, gastrointestinal bleeding or other symptomatic bleeding[26]
- Malignant stroke evolution by day 7[27]
- Symptomatic intracranial haemorrhage by day 7 defined as brain haemorrhage on imaging associated with an increase of at least 4 points in the NIHSS score[28]
- Unexpected intensive care unit admission by day 7
- Mortality by day 7 and day 90
- Procedural feasibility score estimated by the radiologist and the anaesthesiologist and patient acceptability score[29]

Recruitment

Patients are expected to be included during a 2-year period starting in august 2017.

2016-2017: Protocol, approvals from ethics committee (*CPP Sud-Est I*) and the French Medicine Agency (*Agence Nationale de Sécurité du Médicament et des produits de santé, ANSM*); trial tool development (online case report form and randomisation system).

2017-2019: Inclusion of patients.

2019: cleaning and closure of the database, data analyses, writing of the manuscript and submission for publication.

Trial status

The current protocol is version 4.0. Study started enrolment in august 2017. To date (28th October 2018), 186 patients have been randomised in the study.

Patient and public involvement

Patients will not be invited to comment on study design or conduction of the trial.

METHODS: ASSIGNEMENT OF INTERVENTIONS

Allocation and sequence generation

Randomisation will be conducted over a dedicated password-protected, SSL-encrypted website (CSOnline, Clinsight) to allow concealed allocation. Each patient will be given a unique patient number and randomisation number. The allocation sequence will be generated with the use of a minimisation algorithm stratified according to centre, NIHSS score (≤ 15 or > 15) and association of intravenous thrombolysis or not. The participant allocation will be carried out by local investigators who will log into the randomisation system using a personal ID and will enter any relevant information.

Blinding

This is an open label, unblinded trial for the patient and the physician in charge, related to the nature of the intervention (GA with endotracheal intubation or CS). Assessor blinded evaluation of the primary outcome will be performed since the assessor and statistician will be masked to the subjects' assignment group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

At each participating centre, data will be collected and entered into the web-based electronic case report form (eCRF) (CSOnline, Clinsight) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators. From the eCRF, the trial database will be created. Paper case report form will be used in case of technical problems with the eCRF. Trained research coordinators will monitor data collection. Data collected are presented in supplementary file 1.

Patient withdrawal:

Evaluated procedure is tested during endovascular thrombectomy. Nevertheless, participant can withdraw consent at any time without need for further explanation. Data will be destroyed and a new patient will be randomised for the complete sample size.

Statistical methods

Sample size estimation

According to literature analysis based on 5 international randomised controlled trials about endovascular thrombectomy in anterior circulation AIS, frequency of events constitutive of the composite primary outcome was expected at 50%.[1-5] Then, we postulated that 124 patients per group would provide 90% statistical power to detect an absolute between-group difference equals 20% (50% vs. 30%) for a two-sided type I error at 5%. Assuming lost to follow-up and modified intention to treat population requirements (as defined in supplementary file 2) between 5% and 10%, 270 patients have to be recruited for the study.

Interim analysis

A safety interim analysis is planned after 50% of inclusions. The independent Data and Safety Monitoring Board (DSMB) could recommend stopping the study if prolongation of the trial clearly compromises patient safety (in case of serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs)). The steering committee (SC) will be responsible to continue, hold or stop the study based on the DSMB recommendations.

Statistical analysis

A predefined statistical analysis plan will be followed (supplementary file 2). All analyses will be conducted with Stata software (version 13, StataCorp, College Station, USA) and R (http://cran.r-project.org/) before the breaking of randomisation code, in line with the International Conference on Harmonization Good Clinical Practice guidelines. A two-sided p value of less than 0.05 will be considered for statistical significance. Primary analysis will be done in modified intention to treat (mITT). Then, a per-protocol analysis will also be done to take into account protocol deviations notably crossover from CS to GA. Patients who withdraw consent will not be included in these analyses.

Continuous variables will be presented as mean and standard-deviation or as median and quartiles otherwise. Normality will be assessed using the Shapiro-Wilk test and homoscedasticity will be assessed using the Fisher-Snedecor test.

Concerning the comparison of the primary binary composite outcome between CS and GA, a Chi2 test or a Fisher's exact test will be performed as appropriate. Binary outcomes are commonly analysed by applying a logistic regression model to obtain odds-ratios (OR). Although this is often appropriate, there may be situations in which it is more desirable to estimate a relative risk (RR) instead of OR.[30,31] Knol et al. "illustrate the difference between risk ratios and OR using clinical examples, and describe the magnitude of the problem in the literature."[32] Interestingly, the authors reviewed available methods to obtain adjusted risk ratios

and evaluated these methods by means of simulations, and concluded that "The Mantel–Haenszel risk ratio method, log–binomial regression, Poisson regression with robust standard errors, and the doubling-of-cases method with robust standard errors gave correct risk ratios and confidence intervals." Also, adjusted analysis will be conducted with the use of robust (standard errors) random-effects Poisson generalised linear regression (package gllamm) will be used (1) to take into account adjustment on possible confounding covariates selected according to clinical relevance and stratification variables (including stratification parameters) and (2) to consider within and between centre variability (as random-effect). A particular attention will be paid to the covariates used in multivariable regressions, especially quantitative covariates for which convergence issues can be raised due to log-link in the binomial distribution. As presented in statistical analysis plan, only "time delays" will be concerned. Sensitivity analysis considering these covariates, dichotomizing according to the statistical distribution and to the clinical relevance, should be proposed. The results will be presented as relative risks and 95% confidence interval (CIs). The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome.

Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure, this parameter will be treated by different ways according to literature notably as an ordinal variable.[15,33] A shift analysis will also be performed: Cochrane Mantel–Haenszel for the univariate analysis and random-effects ordinal logistic regression adjusted on initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion) for multiple regression.

Concerning the comparisons of secondary outcomes between groups, Student t test or non-parametric Mann-Whitney test as appropriate will be used for quantitative parameters such as intraoperative blood pressure, oxygen saturation, timing delays or length of stays. Chi-squared test or Fisher's exact test will be used for categorical parameters such as NIHSS and ordinal and nominal (dichotomized) mRS, intervention-associated and perioperative complications,

mTICI score, functional independence at day 90 and mortality. Results will be reported as effect-sizes and absolute differences with 95% CIs. Then, multiple regression will be conducted using random-effects models taking into account between and within centre variability: linear mixed models for quantitative endpoints and generalized linear mixed regression for categorical endpoints. The results will be expressed, respectively, as regression coefficients and relative risks, with 95% CIs.

Time-to-event curves will be calculated with the use of the Kaplan-Meier method in univariable analysis. For multiple regression, marginal Cox proportional hazards model (with centre as random effect) will be performed. Proportional hazard assumption will be verified using the Schoenfeld test and plotting residuals. Results will be reported as HRs with 95% CIs.

Concerning the study of parameters collected longitudinally (in particular NIHSS score at day 1 and day 7, arterial pressure and arterial oxygen saturation), mixed models will be used to take into account between and within patient variability, in addition to centre random-effect. The following fixed effect will be analysed: randomisation group, time and their interaction (time x group).

According to clinical relevance and to European Medicines Agency (EMA) and Consolidated Standards of Reporting Trials (CONSORT) recommendations, post-hoc analyses will be proposed after the study of subgroup × randomisation group interaction in regression models (for repeated data or not). Missing values will be notified and analysed. A sensitivity analysis will be performed and the nature of missing data will be studied (missing at random or not). If the frequency is > 5%, additional analyses will be performed using the multiple imputation method. [34]

METHODS: MONITORING

Data monitoring

Before the start of the study, anaesthetic, neurological and radiological medical and paramedical teams are trained at each site for the study protocol by study coordinators. Physicians are in charge of patient screening and inclusion. Patients admitted for stroke treated by endovascular mechanical thrombectomy and not included in the study will be recorded anonymously at each centre into a screening log. Data will be collected in a web-based eCRF by trial personnel. Each centre will only have access to site-specific data. Each patient will receive a unique trial identification number. Only the investigators and research team will have access to any protected health information of study participants and any study data.

Data monitoring and quality control will be conducted in each centre after the first 10 inclusions then after the next 20 inclusions and at the end of the study by official representatives of the study promoter (Department of Clinical Research and Innovation, Clermont-Ferrand University Hospital).

Data will be handled according to the French law. All originals records (including consent forms, reports of SUSARs and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years. Only the principal investigators and the statistician will have access to the final dataset.

Harms

Every adverse events that could be related to the trial will be reported to the trial coordinating centre. According to the French law, all suspected serious adverse events will be reported to the ANSM. The DSMB will also be informed. DSMB is independent from the trial investigators and will perform an ongoing review of safety parameters and study conduct. DSMB members are 2 independent physicians in Anaesthesia / Critical Care Medicine and Neurology, and a Biostatician that have skills and expertise in Anaesthesia, clinical Neuroscience and clinical research. The DSMB will be responsible for safeguarding the interests of trial participants,

assessing the safety of the interventions during the trial and for monitoring the overall conduct of the trial. DSMB could also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. No formal criteria are set to stop the study. However, recommendations for pausing or stopping the study could be made by DSMB in case of SARs and SUSAR. The scientific committee will be responsible for promptly reviewing the DSMB recommendations and to decide whether to continue, hold or stop the study, and to determine whether amendments to the protocol are needed.

ETHICS AND DISSEMINATION

Research ethics approval

The AMETIS study is conducted in accordance with the Declaration of Helsinki and was registered at http://www.clinicaltrial.gov on 25 July 2017 and last updated on 5 September 2017 with trial identification number NCT03229148. The trial was approved by the ethics committee *CPP Sud-Est I* on 22 May 2017 (approval number 2017-11) and ANSM on 6 march 2017 (approval number 2016-A02064-47). Any change to eligibility criteria, outcomes and analyses will be communicated to investigators, the ethics committee and the ANSM to obtain their approval.

Consent or assent

Whenever possible to include the patient, written inform consent will be searched. Nevertheless, related to neurological injury and emergency, the patient may be unable to provide written informed consent. In this case, written informed consent could be obtained from the patient next of kin if immediately available. Otherwise, an emergency consent procedure is used with investigator signature countersigned by an independent physician. As soon as possible after recovery, written informed consent from the patient will be searched to continue the study. This

consent strategy was approved by the Institutional Review Board and the ethics committee *CPP Sud-Est I* on 22 May 2017 in accordance with the 2013 Declaration of Helsinki.

Funding

The study is an investigator-initiated trial with study promotion performed by Clermont-Ferrand university hospital, Clermont-Ferrand, France. There is no industry support or involvement in the trial. This study is supported by grants from the French Ministry of Health (Projet Hospitalier de Recherche Clinique Interrégional 2016). The funders have no influence on study protocol, conduct and results analysis.

Dissemination policy

On study completion, manuscript will be submitted to one peer-reviewed journal regardless of the results. All trial sites will be acknowledged and every investigators name will appear under "AMETIS trial group" in the final manuscript. AMETIS study scientific committee will grant authorship depending on personal input according to the Vancouver guidelines. If a trial site investigator is to gain authorship, the site has to include 30 patients or more. If the site includes 50 patients or more, two authorships will be granted. A writing committee will be composed of members of the scientific committee and investigators to define the order of authors of any publications. Trial results will also be presented at local, national and international meetings.

DISCUSSION

We recently observed the "thrombectomy revolution" in anterior circulation AIS.[35] Emergency interventional procedures in frail stroke patients often require skills from Anaesthesia providers since immobility is needed and severe intra-procedural complications may occur (for example coma, agitation or aspiration pneumonia).

Taking into account the increasing volume of procedures and the potential effect of the anaesthetic strategy on outcome with discrepancy in literature, it appears essential to provide a multicentre randomised controlled trial to enhance external validity as suggested by recent recommandations.[15]

Concurrent ongoing trials with day 90 mRS as a primary outcome are planning to recruit 635 patients to demonstrate non-inferiority between CS and GA,[36] 350 patients to demonstrate superiority of CS vs GS (NCT02822144) or 260 patients to demonstrate superiority of GA vs CS (NCT03263117).

Some limitations could be opposed to the AMETIS trial protocol. First, no specific anaesthetic protocol will be used. We choose this strategy in a pragmatic way since no data demonstrate that a drug is better than another even if modulation of CBF could be variable. However, the protocol requires strict objectives for systolic blood pressure and "normal" blood carbon dioxide tension in GA group.[37,38] Drugs and dose will be monitored. Second, no maximal time delay from stroke onset or maximal/minimal NIHSS values are recommended in order to adhere to a pragmatic investigator-based approach. This strategy complies with recent trials and recommendations: patient selection for thrombectomy is made on angioCT or MRI scans with eventual mismatch evaluation especially when delay is > 6 hours and for wake-up strokes.[15,39,40] Delays and imaging modality used for selection will be monitored. Notably, despite published trials mentioned NIHSS limits as inclusion/exclusion criteria, providing thrombectomy is indicated based on actual recommendations, the optimal anaesthetic strategy deserves evaluation whatever the NIHSS is. Stratification on NIHSS score with a cut-off of 15 will provide homogeneous groups in term of initial severity. As recommended, outcome measures will include adjustments for baseline severity.[15] Third, despite thrombectomy might benefit to patients with premorbid mRS>1, we excluded these patients since evaluation is difficult in emergency condition and inclusion of dependent patients could strongly affect the primary

outcome. This strategy was adopted by others.[3-5,40] Fourth, we choose a composite principal outcome measure since anaesthesia strategy could affect functional independence at 3 months but also peri-interventional morbidity. The effect size that we could expect on functional independence at 3 months is probably far less than thrombectomy on its own. Based on actual literature, SIESTA trial found dramatically decreased functional independence associated with CS with only 18% of mRS 0-2 compared to 37% in GA.[11] 18% of patients being independent is far less than in thrombectomy trials where it barely represents controlled groups (intravenous thrombolysis alone).[1-6] With these proportions, 240 patients would have been necessary to demonstrate a statistical difference with a beta power of 90% but we could expect important centre effect in SIESTA trial. On the contrary, ANSTROKE trial didn't find any difference between groups, with functional independence in respectively 42 and 40% of patients between GA and CS.[12] Based on these 2 trials, functional independence could be obtained in roughly 40% of patients under GA. Providing a 20% variation in positive or negative effect on functional independence, more than 1000 patients would be required with a 80% beta power. An anaesthesia size effect of more than 20% appeared unrealistic.

Fifth, even if possible in selected patients, we will not study local anaesthesia alone. Management solely under local anaesthesia is difficult regarding comfort and immobility particularly in sickest patients, in left hemisphere strokes with aphasia and in tandem lesions (associated cervical carotid artery occlusion). In the CS group, we provide only clinical sedation objectives based on RASS score between 0 and -3. There is no recommended drug to achieve this goal and local anaesthesia is systematically used under CS.

In conclusion, AMETIS trial is the first multicentre randomised controlled study exploring the effect of CS versus GA on functional outcome and peri-procedural complications in endovascular mechanical thrombectomy for anterior circulation AIS. The results of this study could have significant clinical and public health implications.

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AUTHOR CONTRIBUTIONS

RC, EF, SJ, LV, AF and VD are members of AMETIS trial scientific committee and contributed to the conception and design of the research protocol. RC, CFC and EF provided critical skills concerning trial interventions and procedures. CFC and RC wrote the first version of the protocol. RC wrote this manuscript. BP designed the statistical analysis plan. SM, ACL, PFP, SM, BT, CDF, FV, EC, AM, MB, EC and JEB are involved in acquisition, analysis and interpretation of the data. All authors revised the final protocol and approved his submission.

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COMPETING INTERESTS

RC reports personal fees from MSD and Smiths Medical France for education events, transport and accommodation fees from Novartis, Depuy France and Vasopharm outside the submitted work.

KEYWORDS

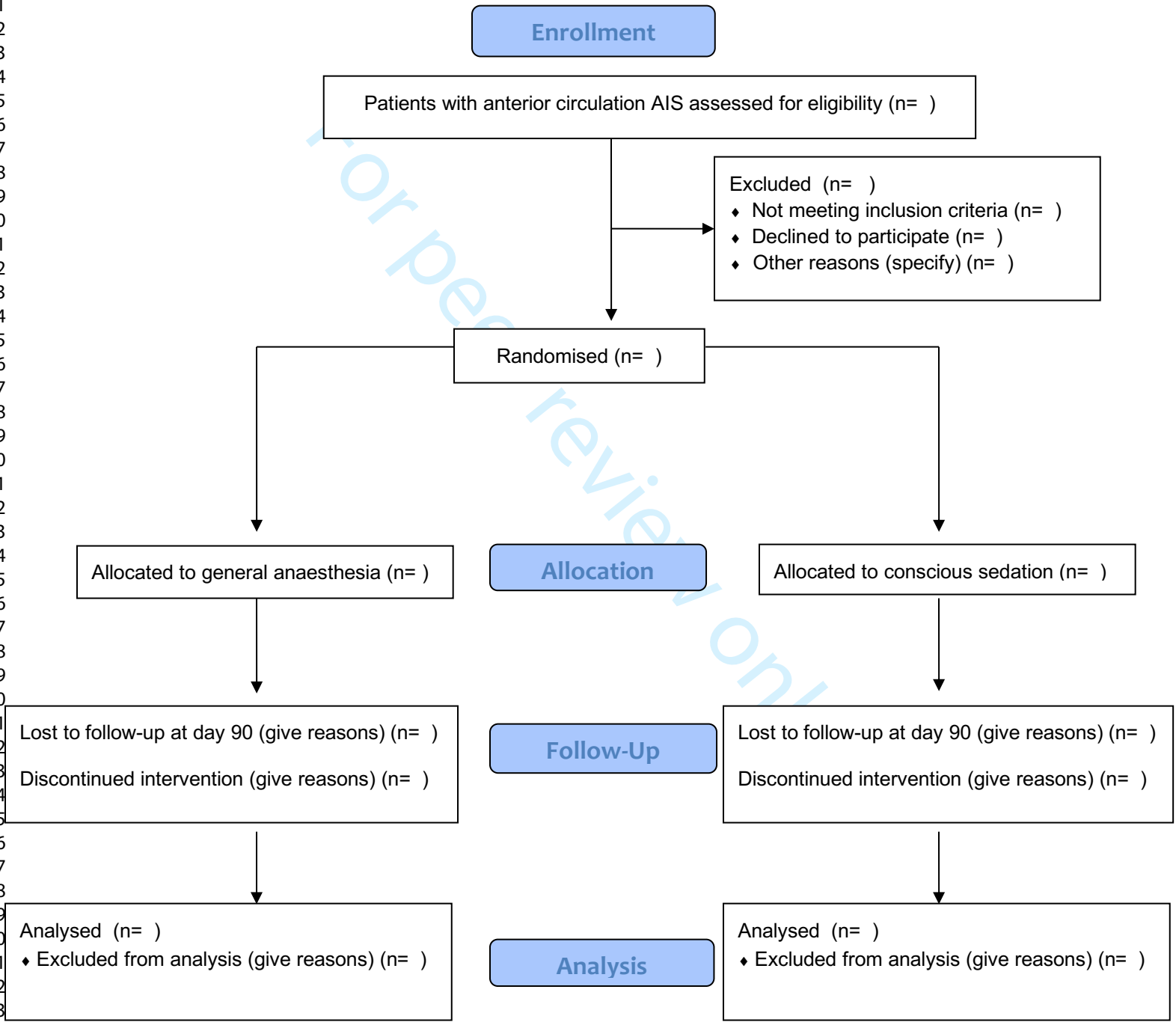
Stroke – Sedation – General Anaesthesia - Thrombectomy

WORD COUNT

3990

FIGURE LEGENDS

Figure 1: CONSORT diagram of the Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial illustrating the randomisation and flow of patients in the study. AIS: Acute Ischemic Stroke



Supplementary file 1: AMETIS trial data collection

At randomisation: Date and time of actual hospital admission, Transfer from another hospital: Y/N, Demographic data (age, height, gender and body mass index), comorbidities (hypertension: Y/N, renal failure: Y/N, cardiac failure: Y/N, diabetes mellitus: Y/N, alcohol abuse: Y/N, active smoking: Y/N, chronic obstructive pulmonary disease: Y/N), ongoing respiratory infection: Y/N, anticoagulation therapy: Y/N, antiplatelet therapy: Y/N, NIHSS score (stratification variable), premorbid mRS, brain imaging used for patient selection with corresponding ASPECT score (MRI: Y/N, AngioCT: Y/N, PerfusionCT: Y/N)[1,2], associated cervical vascular imaging: Y/N, localisation of AIS, intravenous thrombolysis (stratification variable) : Y/N, wake-up stroke: Y/N.

Intraoperative anaesthetic data: date and time of CS/GA, type (Propofol: Y/N, Thiopental: Y/N, Etomidate: Y/N, Midazolam: Y/N, Ketamine: Y/N, inhaled anaesthetics: Y/N, Sufentanil: Y/N, Remifentanil: Y/N, Succinylcholine: Y/N, Atracurium: Y/N, Cisatracurium: Y/N, Rocuronium: Y/N or others) and dose of anaesthetic drugs used, systolic, diastolic and mean arterial blood pressure every 5 minutes until 30 minutes and then every 10 minutes until the end of procedure, hypotension:Y/N (defined as one episode of systolic blood pressure < 120 mmHg during the prespecified time points of blood pressure measurement),[3] maximal blood pressure difference defined as maximal preintervention systolic blood pressure minus minimal perprocedural systolic blood pressure, intraprocedural maximal systolic and diastolic blood pressure, intraprocedural minimal systolic and diastolic blood pressure, pulse oxymetry every 5 minutes for 30 minutes and then every 10 minutes until the end of procedure, RASS score before arterial puncture and at the end of procedure before CS/GA removal, duration of CS or GA, volume of fluids used, type (Norepinephrine: Y/N, Ephedrine: Y/N, Phenylephrine: Y/N or others) and dose of vasoconstrictor if any, type (Nicardipine: Y/N, Urapidil: Y/N or others) and dose of antihypertensive drugs if any, intraprocedural complications (nausea: Y/N,

vomiting: Y/N, aspiration: Y/N, anaphylaxis: Y/N or others), tracheal intubation complication: Y/N, CS conversion to GA: Y/N, feasibility score estimated by the anaesthesiologist at the end of procedure.

Intraoperative neurological and radiological data: date and time of groin puncture and reperfusion if any, date and time of end of procedure (defined as the last set of radiological images), devices used for procedure (stent retrievers: Y/N, contact aspiration: Y/N, intra-arterial thrombolysis: Y/N, stenting: Y/N or others), number of desobstruction attempts, intervention-associated vessel complications (arterial dissection: Y/N, arterial perforation: Y/N, groin hematoma: Y/N, embolization in another arterial territory: Y/N), mTICI score at the end of procedure (ranging from 0 (no perfusion) to 3 (full perfusion with filling of all distal branches)), agitation during procedure (define as a RASS score > +1 at any moment (restless to combative patient) : Y/N), procedure difficulty associated with patient movement: Y/N, complexity of arterial catheterisation: Y/N, altered quality of images: Y/N, feasibility score estimated by the radiologist at the end of procedure.

Procedural time delays: Stroke onset to door delay is time from stroke symptom (or last time seen well for wake-up strokes) to actual hospital admission, Door to groin puncture delay is time from actual hospital admission to groin puncture, Stroke onset to groin puncture delay is time from stroke symptom (or last time seen well for wake-up strokes) to groin puncture, Door to reperfusion delay is time from actual hospital admission to reperfusion, GA/CS induction to groin puncture delay is time from administration of the first anaesthetic/sedative agent to groin puncture, Duration of the procedure is time from groin puncture to end of procedure (defined as the last set of radiological images), Stroke onset to reperfusion delay is time from stroke symptom (or last time seen well for wake-up strokes) to reperfusion (if any).

Postoperative data at day 1 and by day 7 or hospital discharge if prior: NIHSS, groin hematoma: Y/N, pneumonia treated with antibiotics: Y/N, myocardial infarction: Y/N, acute

cardiogenic pulmonary oedema (defined as evidence of fluid accumulation in the alveoli due to poor cardiac function)[4]: Y/N, extra pulmonary infection: Y/N, venous thromboembolism: Y/N, new event of AIS: Y/N, epilepsy: Y/N, gastrointestinal bleeding or other symptomatic bleeding: Y/N, malignant stroke evolution: Y/N, symptomatic intracranial haemorrhage: Y/N, stroke unit and hospital length of stay, unexpected intensive care unit admission: Y/N, care limitation/palliation: Y/N, mortality: Y/N, patient acceptability score.

Postoperative data at day 90: mRS score, hospital length of stay, mortality: Y/N.

1. Pexman JH, Barber PA, Hill MD, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR American journal of neuroradiology* 2001; 22(8): 1534-42.
2. Schroder J, Thomalla G. A Critical Review of Alberta Stroke Program Early CT Score for Evaluation of Acute Stroke Imaging. *Frontiers in neurology* 2016; 7: 245.
3. Schonenberger S, Uhlmann L, Hacke W, et al. Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy: A Randomized Clinical Trial. *Jama* 2016; 316(19): 1986-96.
4. Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *European journal of anaesthesiology* 2015; 32(2): 88-105.

Supplementary file 2: AMETIS trial statistical analysis plan

Populations

Primary analysis will be done in modified intention to treat (ITT). Then, a per-protocol analysis will also be done to take into account protocol deviations notably crossover from CS to GA. Patients who withdraw consent will not be included in the analysis.

Intention-to treat (ITT) population: All randomised patients. This population will not be analysed in the AMETIS study.

Modified intention-to-treat population: All randomised patients except patients who:

- Withdrew consent for the use of data

  OR

- Would never have any of the intervention (CS nor GA, for example due to spontaneous or thrombolytic associated reperfusion after randomisation but before the anaesthetic procedure)

  OR

- Would have the intervention (CS or GA) without any attempt of mechanical thrombectomy due to spontaneous or thrombolytic associated reperfusion.

Per-protocol population: All randomised patients except patients having one or more major protocol violations defined as:

- Patients who would not be eligible for randomization according to inclusion/non-inclusion criteria

  OR

- Patients who accidentally would have received the wrong intervention (CS or GA)

  OR

- Would never have any of the intervention (CS nor GA, for example due to spontaneous or thrombolytic associated reperfusion after randomisation but before the anaesthetic procedure)

  OR

- Would have the intervention (CS or GA) without any attempt of mechanical thrombectomy due to spontaneous or thrombolytic associated reperfusion

  OR

- Patients who would be withdrawn from the protocol because the patient would have withdrawn consent.

Statistical analyses

Primary analysis

Unadjusted Chi-square test (or Fisher's exact test as appropriate) for binary outcome. For rate data, the generalized linear (Stata software: command glm) model will be used with Poisson distribution (link=log and offset), including a random effect to account for centre effect. Results will be expressed as Relative Risks and 95% confidence intervals.

Secondary analyses

- For the primary outcome

Multiple logistic mixed regression will be used with the following covariates (criterion for entering variables tested in the model will be selected if $P<0.10$ and according to clinically relevant covariates with anticipated relationship with outcome), including stratification

parameters, centre treated as a random effect. Particular attention will be paid to the study of multicollinearity.

Binary covariates

- Gender M/F
- Comorbidities Y/N
- Anticoagulation therapy Y/N
- Antiplatelet therapy Y/N
- Intravenous thrombolysis Y/N (stratification variable)
- Wake up stroke Y/N
- Quality of reperfusion: mTICI (good or bad)
- Left sided stroke Y/N
- Carotid top occlusion Y/N

Continuous covariates (with logarithmic transformation when appropriate)

- Demographic data
- Time delays

Ordinal covariates

- NIHSS score (stratification variable)
- Baseline mRS
- ASPECT score
- Localisation of AIS
- mTICI score

- For secondary outcomes

A chi-squared test (or Fisher's exact test, as appropriate) will be used for secondary binary outcomes. The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome (mRS score 0 to 2 by day 90, perioperative complications: intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7). Adjusted analyses will be performed with the use of random-effect Poisson generalized linear model regression and will be presented as Relative Risks and 95% confidence intervals, using the same adjustment variables.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired t test or the Mann-Whitney U test as appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Adjusted analyses, using multiple linear regression, will be conducted using the same adjustment variables and center as random-effect. Results will be expressed as regression coefficients and 95% confidence intervals.

Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure, this parameter will be treated by different ways according to literature notably as an ordinal variable. A shift analysis will be also performed with Cochrane Mantel–Haenszel for the univariate analysis and random-effects ordinal logistic regression adjusted on initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion) for **multiple regression**.

Time-to-event curves will be calculated with the use of the Kaplan-Meier method in univariable analysis. For **multiple regression**, marginal Cox proportional hazards mode, with centre as random-effect, will be performed with results reported as hazard ratios with 95%

confidence intervals, and proportional hazard assumption verified using the Schoenfeld test and plotting residuals.

Concerning the study of the parameters collected longitudinally, mixed models will be used to take into account between and within patient variability, in addition to centre random-effect. The following fixed effect will be analysed: randomisation group, time and their interaction.

Planned subgroup analyses will be done to explore potential influence of age, stroke laterality, stroke initial severity based on NIHSS, time delay, thrombus location and associated extracranial carotid artery stenosis/thrombosis on the incidence of the primary outcome. The study of interaction between randomization group and subgroup will be analysed.

If missing data are greater than 5%, an additional analysis will be performed using the multiple imputation method (Stata software, command mi).

A two-sided P value of less than 0.05 will be considered for statistical significance.

As proposed by some statisticians,[1,2] a particular focus will be given to the magnitude of differences, in addition to inferential statistical tests expressed using p-values.

Outcomes

Primary outcome measure: The primary outcome measure is a composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary outcome measures:

- Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure[3,4]:
  - Ordinal score on the mRS by day 90
  - Functional independence by day 90 defined as a mRS score 0-2
  - Excellent recovery by day 90 defined as a mRS score 0-1
  - Moderate recovery by day 90 defined as a mRS score 0-3
  - Shift analysis of day 90 mRS adjusted for initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion)
  - Good recovery defined with sliding dichotomy responder analysis relating day 90 mRS with baseline NIHSS score: mRS 0 for NIHSS ≤ 7; mRS 0-1 for NIHSS 8-14; mRS 0-2 for NIHSS > 14
- Intraprocedural hemodynamic and ventilatory conditions and complications defined as hypotension, blood pressure variability, hypoxemia and aspiration
- Intervention-associated vessel and others complications defined as arterial dissection or perforation, groin hematoma, embolization in another arterial territory
- Stroke onset to door delay, door to groin puncture delay, door to reperfusion delay, stroke onset to groin puncture delay, GA/CS induction to groin puncture delay, duration of the procedure, stroke onset to reperfusion delay
- Successful reperfusion defined by the modified Treatment In Cerebral Ischemia (mTICI) reperfusion scale of 2b or 3 (with a grade of 2b or 3 indicating reperfusion of > 50% of the affected territory)
- NIHSS by day 1 and day 7
- Stroke unit and hospital length of stay

- Perioperative complications by day 7 defined as pneumonia, acute cardiogenic pulmonary oedema, myocardial infarction, extra pulmonary infection, venous thromboembolism, new event of AIS, epilepsy, gastrointestinal bleeding or other symptomatic bleeding
- Malignant stroke evolution by day 7
- Symptomatic intracranial haemorrhage by day 7 defined as brain haemorrhage on imaging associated with an increase of at least 4 points in the NIHSS score
- Unexpected intensive care unit admission by day 7
- Mortality by day 7 and day 90
- Procedural feasibility score estimated by the radiologist and the anaesthesiologist and patient acceptability score

1. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990; 1(1): 43-6.
2. Feise RJ. Do multiple outcome measures require p-value adjustment? *BMC medical research methodology* 2002; 2: 8.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018.
4. Nunn A, Bath PM, Gray LJ. Analysis of the Modified Rankin Scale in Randomised Controlled Trials of Acute Ischaemic Stroke: A Systematic Review. *Stroke research and treatment* 2016; 2016: 9482876.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5 and 19
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	19
Protocol version	#3	Date and version identifier	13
Funding	#4	Sources and types of financial, material, and other support	See note 1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 and 2

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	See note 2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See note 3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15 and 19
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7 and 8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7 and 8
Objectives	#7	Specific objectives or hypotheses	8 and 9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10 and 11

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11 and 18
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10 and 11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	See note 4
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14, 15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	See note 5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	See note 6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	See note 7
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18 and 19

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	26 and 27
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases,	20 and 21

		or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Author notes

1. 20, 26 and 27
2. 1, 2 and 20
3. 20, 25, 26, 27 and
4. 11, 12 and 13
5. 16, 17 and supplementary file
6. 17 and supplementary file
7. 18 and supplementary file